# New Methods for the Synthesis of Biologically Active Phenanthridine-Based Libraries

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## *DECLARATION*

This thesis is submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Edinburgh. Unless otherwise stated the work in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualification at this, or any other university. In accordance with the regulations this thesis does not exceed 70,000 words in length.

Lauren Rona Donaldson

*For Mum, Dad, Neil and Finn.*

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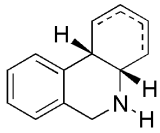
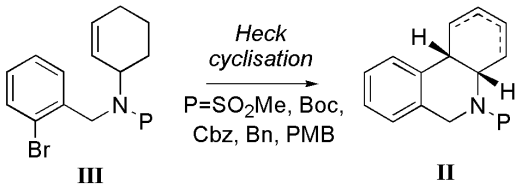
## *ABSTRACT*

Small molecule libraries have become essential for the development of drug discovery campaigns and chemical genetics. The studies towards the synthesis of a small molecule library, based upon the *cis*-ring fused phenanthridine core **I**, will be described.



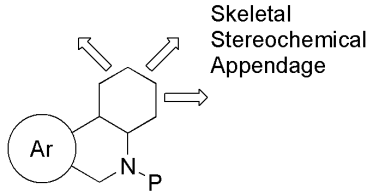
**I**

The first section of this thesis examines the development and application of a novel intramolecular Heck cyclisation to the synthesis of core phenanthridine structure **II**, via precursor **III** (**Chapter 2**).




**III** **II**

The second section (**Chapter 3**) describes the extension of this methodology towards the development of a library of phenanthridines **IV**. This includes methodology designed to incorporate the key principles of diversity-oriented synthesis, namely appendage, stereochemical and skeletal diversity.




**IV**

The final part of this thesis (**Chapter 4**) describes the merging of these various methodologies to generate a small library of novel phenanthridine analogues. Preliminary biological evaluation of the phenanthridine library using whole organism zebrafish phenotyping, will also be discussed.

*CONTENTS*

# *INTRODUCTION*
# CHAPTER ONE

## METHODS FOR THE SYNTHESIS OF BIOACTIVE SMALL MOLECULE LIBRARIES

### 1.1 Chemical libraries

Modern drug discovery relies upon small molecule libraries to generate potential leads through the process of high-throughput screening.[1] These libraries are screened against a pre-validated biological target and any suitably active compounds (known as hits), are subjected to further development in lead optimisation (**Figure 1.1**).

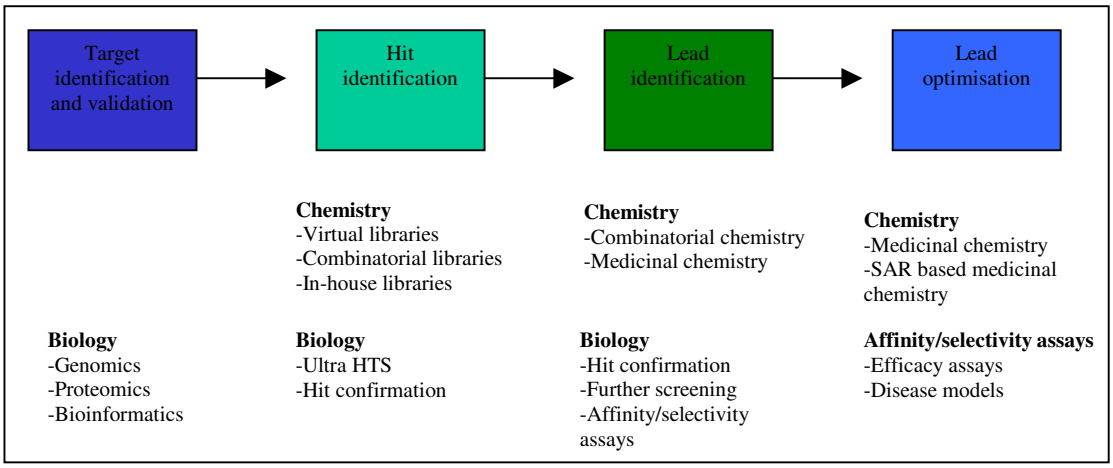



**Figure 1.1** *The process of modern drug discovery.*

More recently, compound libraries have been required to further the field of chemical genetics, an area that seeks to emulate the success of classical genetics by using small molecules to probe the function of proteins. This can be performed in a forward or reverse manner as depicted in **Figure 1.2**.[2,3] Forward chemical genetics involves identification of a phenotype in an organism or cell that is caused by a small molecule, in the example shown the mitotic spindle is in disarray. The protein target that has been modulated can then be identified, hence providing its function and a small molecule modulator from one process. Reverse chemical genetics involves the selection of a protein target (here a Lux-R type protein), against which small molecules are screened for candidates that affect the protein's activity (here pigment production). In this reverse sense, by observance of the arising phenotype, the

function of a protein can be determined. This is akin to classical drug discovery, but in this case the function of the protein is not known beforehand.

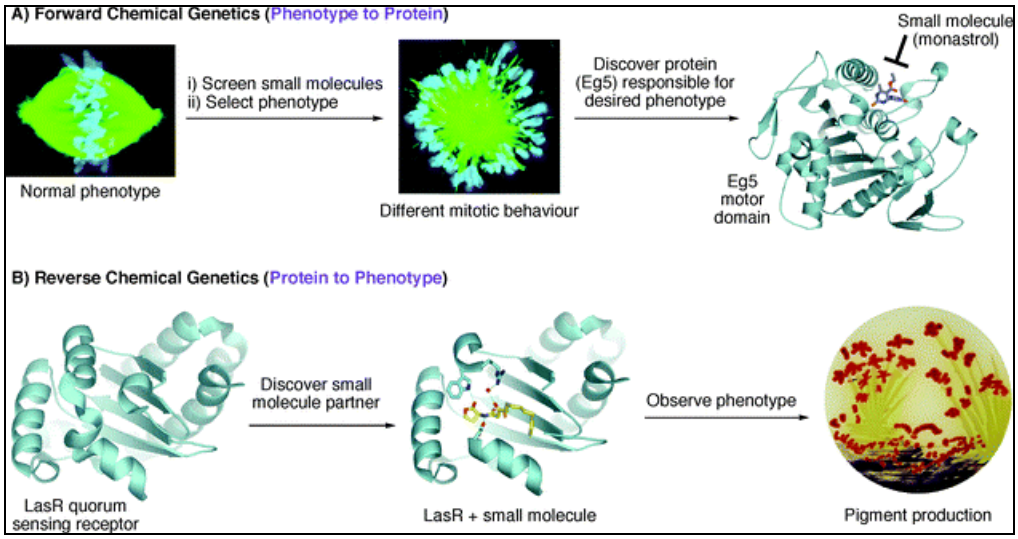



**Figure 1.2 A** *Forward chemical genetics.* **B** *Reverse chemical genetics.*[3]

A) A small molecule binds to the Eg5 motor protein causing disarray of the mitotic spindle (tubulin green, DNA blue). B) An agonist binds to a Lux-R type protein activating pigment production.

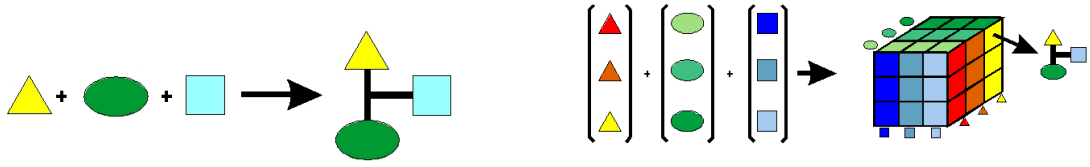
The ultimate goal of chemical genetics is to identify small molecules that perturb the function of every gene product, this is known as chemical genomics. Approximately 10% of the human genome (25,000 genes) is thought to encode proteins that will bind drug-like compounds, and of these only 1000 have a known small molecule chemical modulator.[3] In addition, for all the approved therapeutic drugs, only 324 biological targets have been identified, therefore the potential for research in this area is huge.

Both chemical genetics and modern drug discovery processes put demands on the need for small molecule libraries. Library sources can be found in the form of in-house compound collections,[3] commercially acquired libraries from combinatorial chemistry campaigns,[2] or even virtual libraries.[4] However, many such libraries suffer from a lack of diversity as a result of their origin. For example, pharmaceutical in-house compound collections can be biased as a result of the previous projects

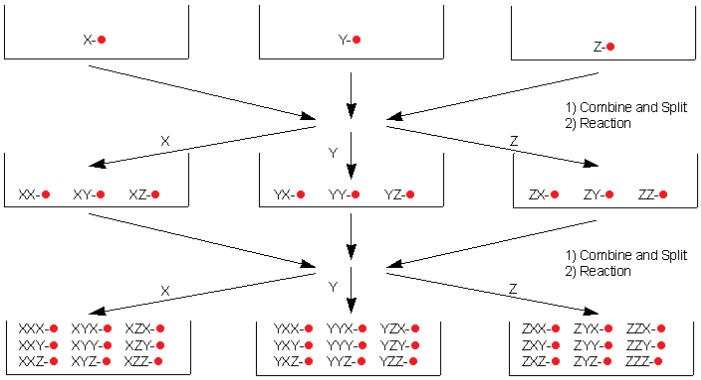
undertaken in the company and by specific guidelines such as Lipinski's rules.[γ] Therefore recently there has been renewed interest in compound libraries derived from natural products,[5] and in libraries synthesised with the aim of maximising structural and skeletal diversity such as diversity-oriented synthesis (DOS) libraries,[3] and biologically-oriented synthesis (BIOS) libraries.[6] Approaches towards these different types of library synthesis will be addressed in this chapter.

## 1.2 Advances in combinatorial chemistry

Combinatorial chemistry enables the rapid assembly of collections of small molecules, usually using a solid support.[7] Compared to target-oriented synthesis, combinatorial chemistry allows multiple reactions to be performed in parallel using different building blocks to access a diverse range of products (**Figure 1.3**). In combination with solid-phase split-pool chemistry, the rapid assembly of small molecule collections in high yield is possible.



**A** **B**




**C**

**Figure 1.3** *Single molecule* (**A**)*, combinatorial* (**B**) *and* (**C**) *split-pool synthesis.*[7]

[γ] Lipinski's analysis of the world drug index led to the 'rule-of-five', which identifies key properties considered appropriate for small molecules intended for oral administration. These properties are: molecular mass <500 Da, number of H-bond donors <5; number of H-bond acceptors <10; octanol-water partition coefficient <5.[8]

These small molecules can then be screened as mixtures following cleavage from the solid-support, and any active hits can be deconvoluted and resynthesised individually using the existing route. More recently a wealth of technology has been developed to facilitate faster, cleaner and more robust synthesis, for example the use of automated microwave reactors to perform many reactions in sequence.[9] Other areas include automated weighing devices, LCMS and NMR systems for automated sample analysis, and radio-frequency tagging or optical coding to track each specific compound throughout the synthesis process.[10] Similarly, computer systems have been developed to manage the library and keep track of every compound synthesised, along with its purity and location, removing the need for human intervention to a large extent.[9]

At its outset, combinatorial chemistry promised the synthesis of libraries comprising millions of compounds, which would rapidly accelerate the drug discovery hit to lead optimisation stage. However, more recently, questions have been raised as to whether this approach really fulfilled its promise, since some of the libraries produced few or no hits.[11] Although the libraries created by combinatorial chemistry campaigns were large and structurally diverse from each other, compound members within a library were less so, as a result of the similar building blocks and reaction sequences used to construct them. As a result of this, the focus of library synthesis has shifted toward approaches that enable the introduction of greater structural diversity and wider population of chemical space.[12]

### 1.3 Chemical space

Chemical space refers to the infinite number of chemical substances that in principle can be synthesised. Calculations have estimated this to represent approximately $10^{60}$ drug-like compounds, an unachievable number when considered there are only $10^{51}$ atoms on earth.[13] Chemical space can be represented in 3D using different molecular descriptors as the three axis, where descriptors are characteristics of compounds such as molecular weight.[14] The chemical space explored by three different approaches to complex molecule synthesis are illustrated by the axes shown in **Figure 1.4**.

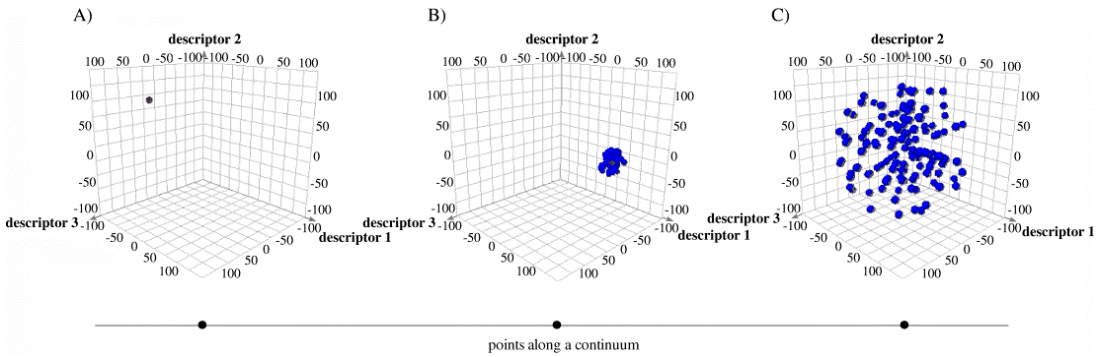



**Figure 1.4** *Exploration of chemical space by Target-oriented synthesis* (**A**)*, Focused library synthesis* (**B**) *and DOS* (**C**).[14]

Within chemical space there are voids where there are no molecules of biological interest, but likewise there are areas that correlate to excellent bioactivity.[3] Several different approaches have been developed to try and identify the regions of chemical space for which the likelihood of obtaining biologically active compounds is given, or at least enhanced.

A recent principal component analysis, based on several molecular descriptors (number of chiral centers, rotatable bonds, C-N bonds, C-S bonds. C-O bonds, C-X bonds, degree of ring fusion, ratio of aromatic rings to ring atoms) showed that natural products and drug compounds occupied far greater areas of chemical space than combinatorial libraries (**Figure 1.5**).[15] This suggests that the best chance of identifying bioactive molecules lies with a library that depends not on size, but on the quality and diversity of its components. The majority of approaches currently being investigated in the literature make use of natural products to varying degrees, as inspiration for the synthesis of high quality and diverse libraries.

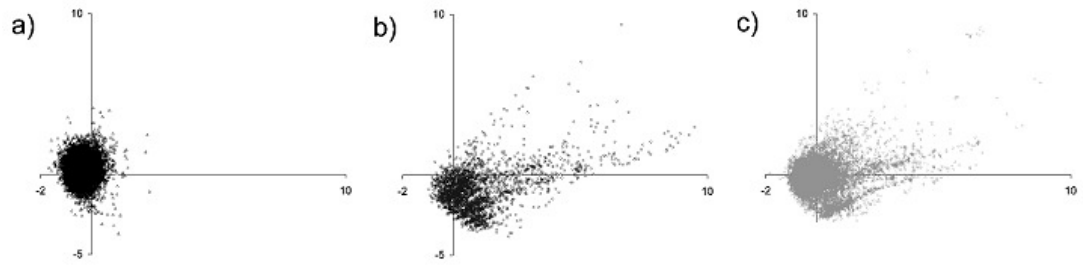



**Figure 1.5** *Principle component analysis of a) a random selection of combinatorial compounds; b) natural products; c) approved drugs.*[15]

### 1.4 Natural product based library synthesis

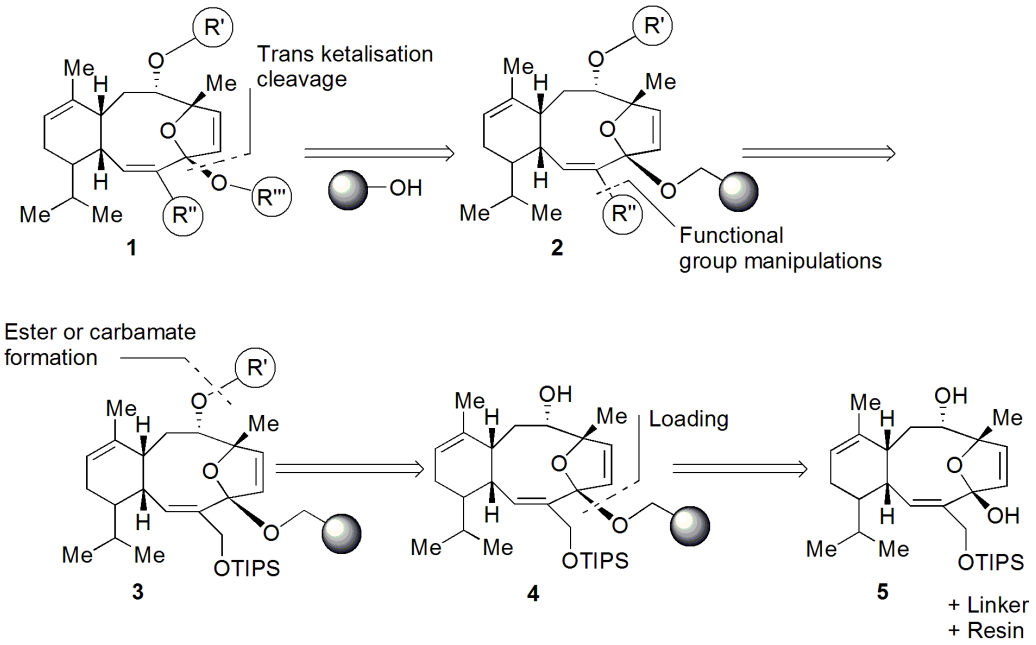
Despite the intrinsic bioactivity of natural products, their use in drug discovery libraries has been neglected over recent years.[5] Much of this can be attributed to their structural complexity, which rendered them incompatible with high-throughput synthesis for many years, and difficult to modify into analogues. Natural products are also notoriously difficult to obtain and purify, and so are often screened as mixtures that are difficult and time-consuming to deconvolute. Additionally, despite natural products being used clinically to great success, they do not tend to lie within the parameters dictated by Lipinski's rules,[8] making them less favoured as potential drug leads.

However, despite these drawbacks, natural products still possess a higher hit-rate in drug discovery than any unspecific library. For example, between 1981 and 2002, 61% of the 877 new chemical entities approved by the FDA were natural product-based.[16] Nature designed these molecules for a specific biological purpose and function, and given the close relationship shared by the genomes of all organisms, evolution selected natural products to bind to proteins similar to human proteins.[11] Despite the recent lack of interest from mainstream pharmaceutical companies, natural product synthesis has formed the basis of much of the organic synthetic literature.[17] As a result, many new pieces of methodology for manipulation and generation of these complex architectures have been reported, along with several reports of solid phase total synthesis.[11] Additionally, advances in microbial genomics,[5] and separation/purification technology have made the prediction, identification and isolation of natural products less challenging.[18,19]

Natural products are unmatched in terms of their inherent bioactivity and their ability to probe chemical space.[5] Therefore they offer excellent, biologically validated starting points upon which to base chemical library design. The three main ways in which this has been investigated will be discussed below.

### 1.4.1 Libraries based on the core scaffolds of individual natural products

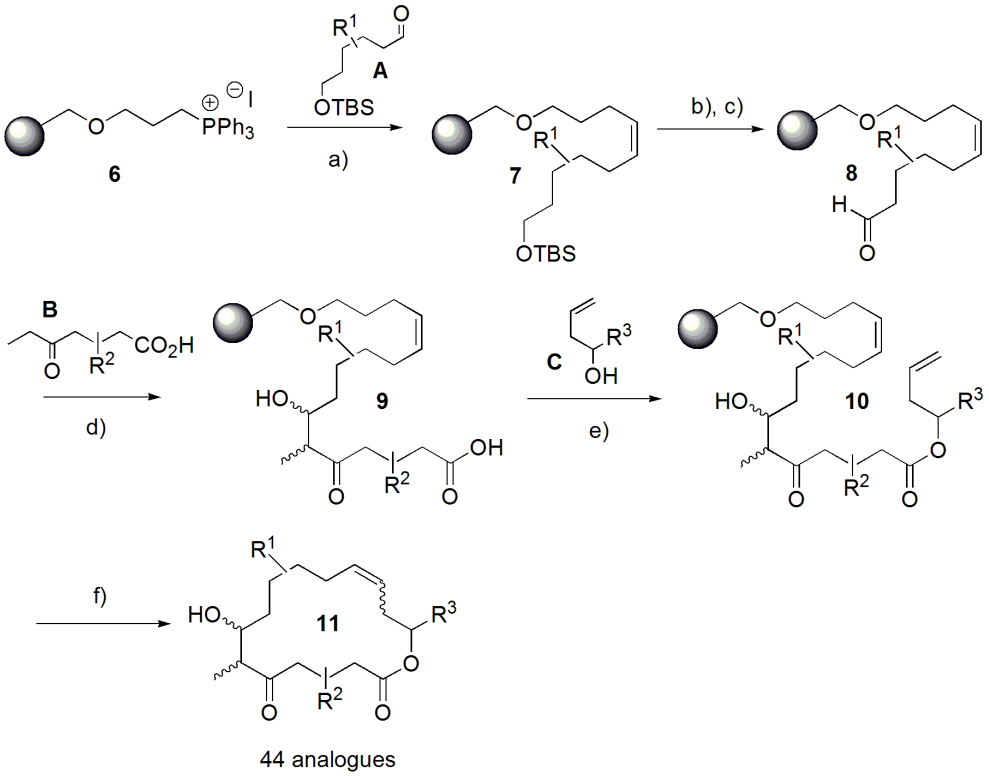
Libraries based on the core scaffolds of individual natural products are a useful way of optimising the activity of a parent compound, and establishing structure-activity relationships.[20] Fortunately, the combinatorial methods that caused the initial decline of natural product screening are now proving highly useful for this type of library synthesis. Typically, complex natural product skeletons (usually derived from total synthesis or semi-synthesis efforts) are immobilised on solid support, thus enabling relatively simple derivatisation.[5,21] This method was used to prepare a library of analogues closely based on the anti-tubulin natural products sarcodictyin A and B (**Scheme 1.1**).[22] In this example, immobilisation of advanced intermediate **5** on a solid support enabled the introduction of diversity at three points (R', R'' and R''') on the core structure. A small library of 30 analogues was prepared, with several showing equal or better activity than the parent structures, including against taxol-resistant cancer strains.




**Scheme 1.1** *Solid phase synthesis of a 30-member focused library of sarcodictyin analogues.*[22]

An alternative approach to libraries of this type can be realised by making use of a synthetic route developed during the original natural product synthesis. If this pre-established chemistry is compatible with solid support, multi-component building

blocks can be used to rapidly build a focused library of analogues.[21] This approach was successfully used for the generation of a 44-member library based on the natural products epothilone A and B (**Scheme 1.2**).[23] The epothilones share their unusual anti-mitotic mode of action with paclitaxel, however they possess a more accessible core structure and have the advantage of being several-thousand times more active against paclitaxel resistant cell lines.[24] The epothilone library was derived using radiofrequency tagged Merrifield resin that enabled sorting and tracking of intermediates throughout the split-pool synthesis. The key step involved simultaneous formation and release of the lactone macrocycle **11** by a ruthenium carbene-catalysed ring-closing metathesis reaction. Nine of the synthesised analogues showed cytotoxic activity against breast and ovarian cancer cells.




**Scheme 1.2** *Solid phase-SMART microreactor synthesis of a 44-member epothilone library.*[23]

a) i) NaHMDS (3 eq), THF:DMSO 1:1, 25 °C, 12 h; ii) **A** (2 eq), THF, 0 °C, 3 h; b) 0.2 M HCl in THF, 25 °C, 12 h; c) $(COCl)_2$ (4 eq), DMSO (8 eq), $Et_3N$ (12.5 eq), -78 → 25 °C; d) i) **B** (2 eq), LDA (2.2 eq), THF, -78 → - 40 °C; ii) $ZnCl_2$ (2 eq), -78 → -40 °C, 2 h; e) **C** (5 eq), DCC (5 eq), DMAP (5 eq), 25 °C, 15 h; f) Grubbs I (0.2 eq), $CH_2Cl_2$, 25 °C, 48 h.

Individual natural products have also been the inspiration for libraries used to address a variety of biological targets.[20] This approach works on the proposal that libraries based on a natural product that is known to bind one particular protein domain should be a rich source of compounds that bind selectively to other targets sharing the same protein fold.[11] This is known as biologically oriented synthesis (BIOS) and is discussed in a separate section below (see **section 1.6**).

### 1.4.2 Libraries based on specific substructures from classes of natural products

Specific substructures of natural products can also be considered biologically validated, and libraries based on these foundations are becoming increasingly popular. The concept of a 'scaffold tree' was recently reported as a method for categorising natural product substructures.[6] Stepwise deconstruction of complex structures into smaller parent structures was achieved using a set of rules derived from organic and medicinal chemistry. This maps the underlying scaffolds of natural products in a hierarchical manner based upon their cyclic frameworks and linkers (**Figure 1.6**). Within the scaffold tree, three scaffold classes are distinguished: carbocycles, *N*-heterocycles and *O*-heterocycles, with the most common scaffolds comprising of two to four rings.

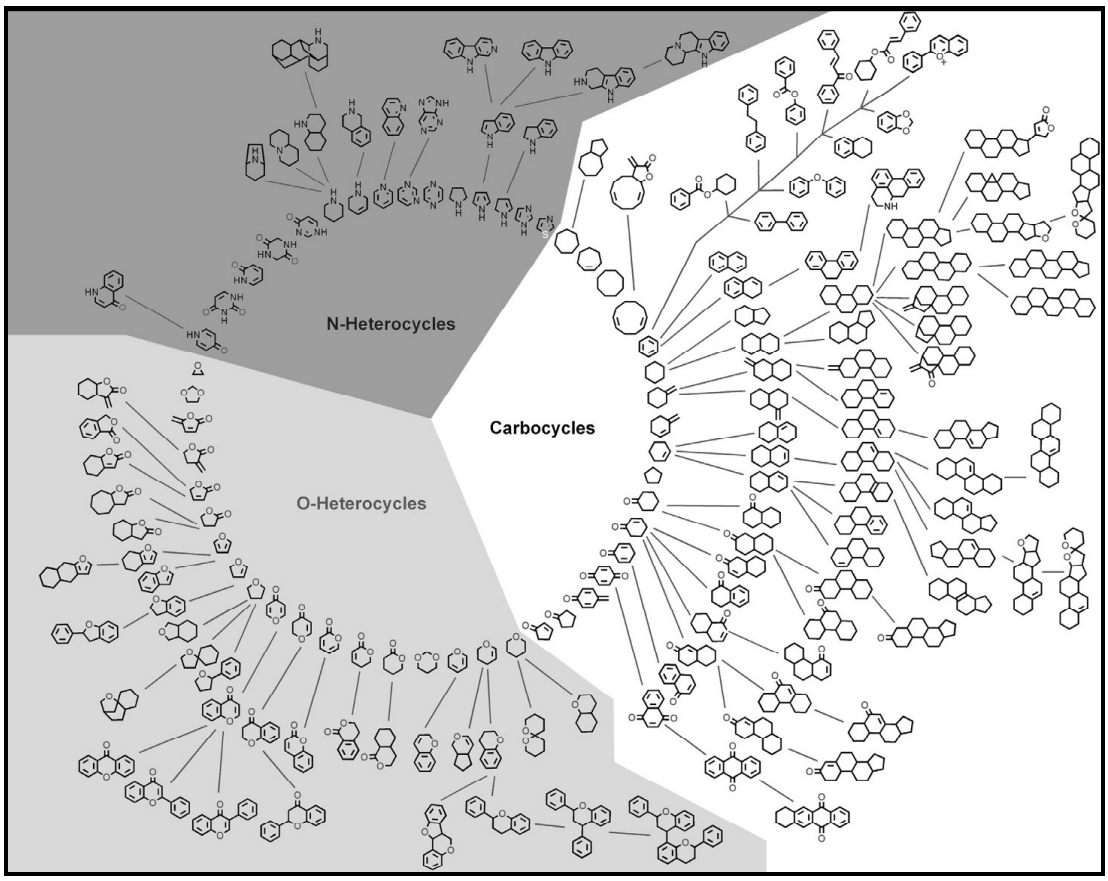
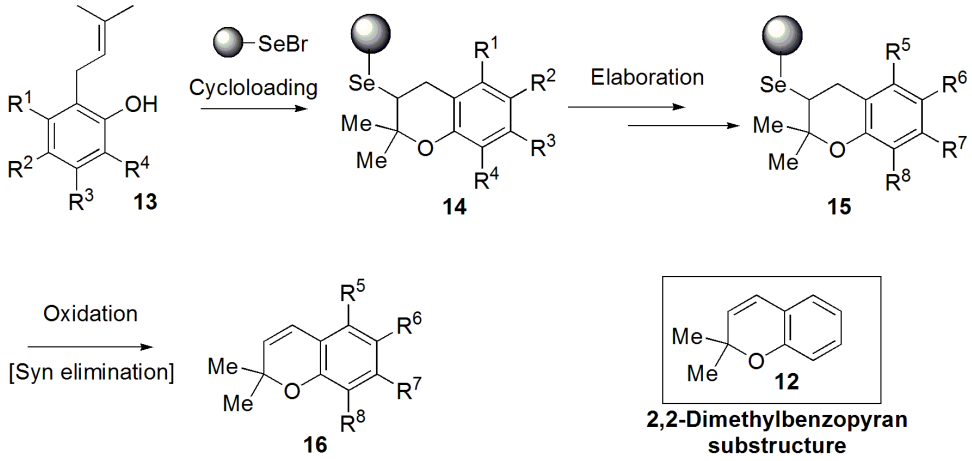



**Figure 1.6** *A scaffold tree generated in the structural classification of natural products (SCONP).*[6]

The significance of this approach lies in its ability to enable correlation between different classes of scaffold, which is performed during BIOS (**See section 1.6**).[6] It also enables the identification of biologically relevant core scaffolds for the design and synthesis of focused library collections. Such libraries are enhanced by their natural product origins, but also have the added benefit of increased structural diversity so that a wider range of biological targets might be addressed.

One of the earliest examples of this type of substructure-based focused library synthesis incorporated the 2,2-dimethylbenzopyran unit **12** (**Scheme 1.3**).[21,25,26] This structural motif lies at the heart of many natural products including the flavenoids, stillbenoids, coumarins, rotenoids and the chromene glycosides, several of which have important medicinal applications. Initial efforts were concentrated on the combinatorial split-pool synthesis of six focused libraries, based around 2,2-dimethylbenzopyran targets of recent biological interest. This resulted in the development of novel solid-phase selenium-based cycloloading methodology for the

construction and elaboration of structures containing this template (**Scheme 1.3**).[21] The selenyl bromide resin encompassed the essential features of both a solid-phase reagent and a traceless linker, eliminating the presence of any residual functionality in the product structure upon oxidative cleavage from the resin.




**Scheme 1.3** *Solid-phase synthesis strategy for the loading, elaboration and cleavage of 2,2-dimethylbenzopyrans.*[21]

This novel methodology was then applied in conjunction with the IRORI NanoKan optical encoding system, to synthesise a 10,000 member library containing approximately 1-2 mg of each small molecule.[25] The library was then subjected to comprehensive biological screening, followed by parallel solution-phase optimisation to increase the number and diversity of library members, and aid identification of key structure activity relationships.[26] As a result, several cyanostilbenes were identified which had low micromolar activity against MRSA, including compound **17** (**Figure 1.7**) which exhibited a 5 μM MIC (minimum inhibitory concentration) against six different MRSA strains. Another screen identified novel anti-steroidal agonists of the farnesoid X reporter gene, including compound **18**, fexachloramide, which displayed an $EC_{50}$ value of 188 nM. While the active compounds are not potent enough to represent drug candidates, they do offer new avenues for lead optimisation and exploration.

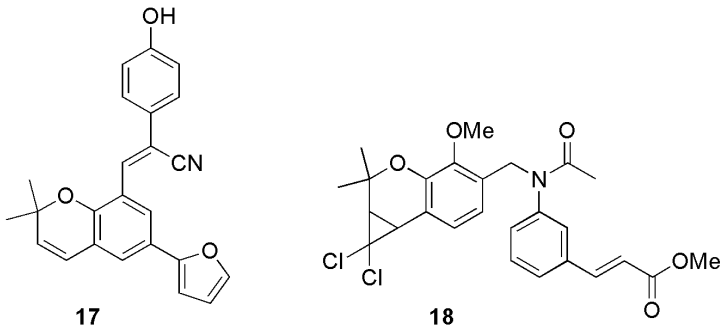



**Figure 1.7** *Bioactive compounds discovered from the synthesis of a 10,000-member library based on a 2,2-dimethylbenzopyran core.*[21,25,26]

### 1.4.3 Libraries based on the general characteristics of natural products

Libraries can also be synthesised using the general structural characteristics of natural products, rather than their specific structures or substructures. Natural products show bioactivity because their rigid structures are able to present functional groups in a favourable arrangement. Therefore mimicking the complex structures of natural products by the incorporation of dense stereochemical and functional diversity around a rigid molecular skeleton may lead to the identification of novel pharmacophores.[20] Although this approach forgoes any direct connection to specific natural product structures, it does offer a unique opportunity for the synthesis of novel small molecules that may be able to address targets currently considered undruggable.

This type of library synthesis was applied to the 1,3-dioxane structure illustrated in **Figure 1.8**.[27] The 1,3-dioxane was chosen due to its structural rigidity and its reproducible stereoselective synthesis in the presence of diverse ancillary groups. Initial efforts focused on the synthesis of a 1890-member pilot library using solid-phase split-pool chemistry in conjunction with various building blocks.

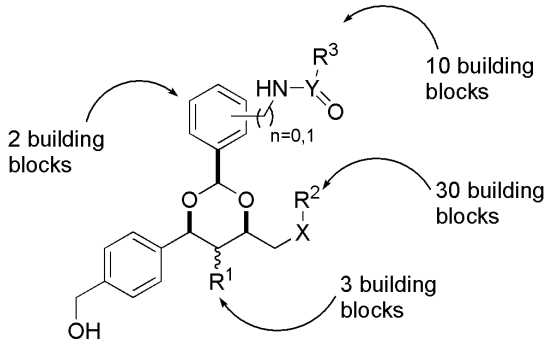



**Figure 1.8** *1,3-dioxane library overview.*[27]

From this library several bioactive compounds were identified including uretupamine B **19**, a novel inhibitor of the yeast nutrient responsive signaling proteins Ure2p (**Figure 1.9**). Two selective inhibitors of the histone deacetylase (HDAC) family were also discovered, tubacin **20** and histacin **21**. This led to the identification of a new potential antimetastatic and antiangiogenic therapeutic target, HDAC6.[27]

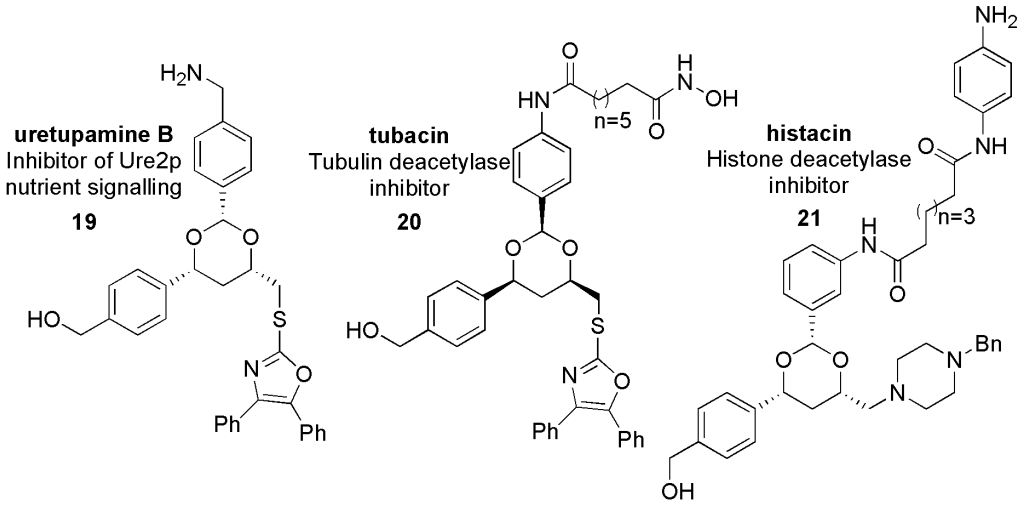
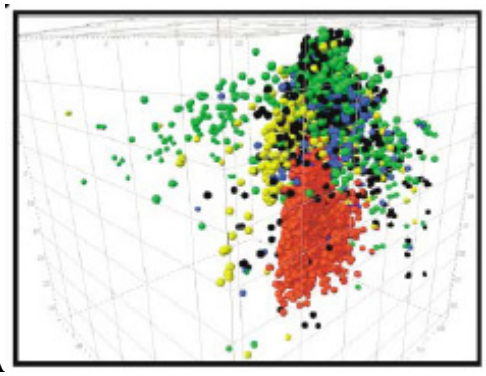


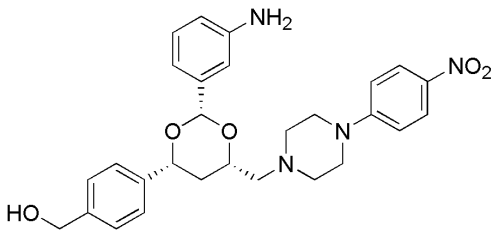

**Figure 1.9** *Bioactive small molecules discovered from 1890-member 1,3-dioxane based library.*[27]

More recently, this 1,3-dioxane library was expanded to 18,000 members through the incorporation of additional building blocks and stereochemical diversity. Principal component analysis assessed that the 18,000-member library explored an equivalent volume of chemical space to a known library of 2000 bioactive compounds (**Figure 1.10 A**).[28] From the biological screening results, compound **22** (**Figure 1.10**, **B**) was shown to have a detrimental effect on cardiovascular development in embryonic

zebrafish, whereas its enantiomer, synthesised in the earlier library, did not. This illustrates the dividends of stereochemical library enrichment.



**A**




**22**
Inductor of cardiac malfunction
in developing zebrafish

**B**

**Figure 1.10** *Stereochemical enrichment of a 1,3-dioxane library.*[28]

**A**: 1,3-dioxanes (red) and a known bioactive library (various colors) plotted in molecular diversity space. **B**: Compound **22** induces cardiac malfunction in zebrafish while its enantiomer does not.

Libraries constructed in this manner are termed by some to be diversity-oriented synthesis (DOS) around a privileged structure. Likewise, libraries synthesised around a natural product substructure could also technically earn this name. There is a fine line between these different approaches that tend to be described in different ways by different authors. However, for the purposes of this overview, DOS will refer to library synthesis governed by the specific rules and thought processes described in the next section (**1.5**).

## 1.5 Diversity-oriented synthesis (DOS)

It is clear from the natural product-based examples reported above (**section 1.4**) that the more complex and diverse a library is, the greater its chances are of producing a novel bioactive small molecule. The field of diversity-oriented synthesis was developed with the aim of creating structurally diverse libraries of architectures that mimic the overall complexity of natural products.[14] The goals of DOS include the development of pathways that lead to the synthesis of collections of small molecules in three-to-five steps. These pathways must allow the incorporation of skeletal and stereochemical diversity by the use of complexity-generating reactions, and ideally lead to molecules with defined coordinates in chemical space. DOS methodology should also allow the incorporation of different building-blocks from the outset, and additionally create sites for the potential appendage of further building-blocks post-screening, so that active hits might be optimised.

### 1.5.1 Forward-thinking synthetic analysis

In contrast to target-oriented synthesis that employs retrosynthetic analysis, DOS makes use of forward synthetic planning to move in the direction of simple and similar structures to complex and diverse structures (**Figure 1.11**).[14]

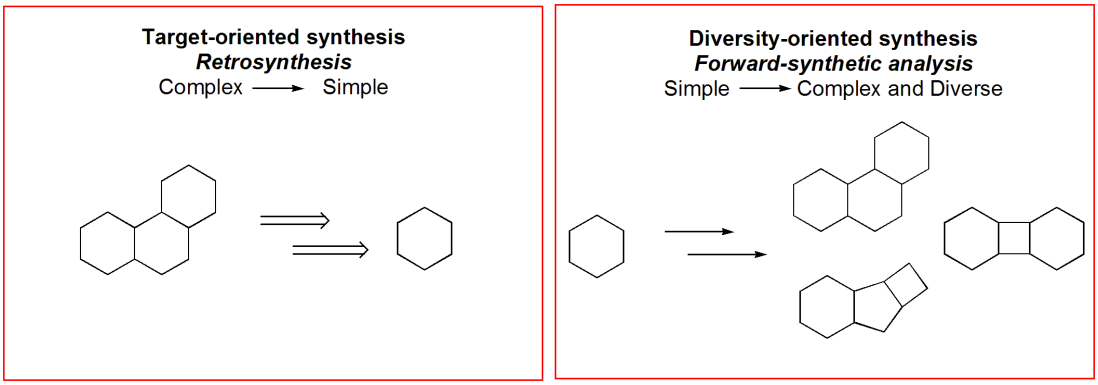


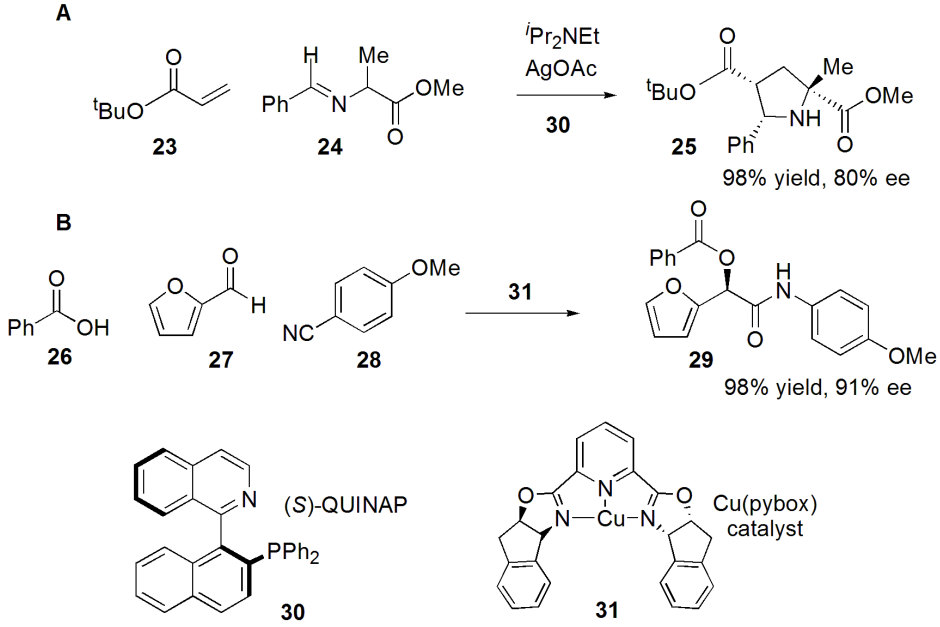

**Figure 1.11** *Retrosynthetic analysis versus forward-synthetic analysis.*[14]

The key subunits of retrosynthesis are the 'retrons' that must be identified before the application of a transformation. In contrast, the key subunit of forward-synthetic analysis is the transformation itself, which enables the conversion of a group of substrates into a group of products.[14] The key element for the implementation of forward-synthetic analysis is the identification of reactive subunits common to a

group of compounds, which enables them all to be potential substrates for the same reaction. DOS makes use of both complexity-generating reactions, and diversity-generating processes in its quest to populate chemical space, both methods can be considered independently, and will be discussed below.

### 1.5.2 Complexity generating reactions (simple → complex)

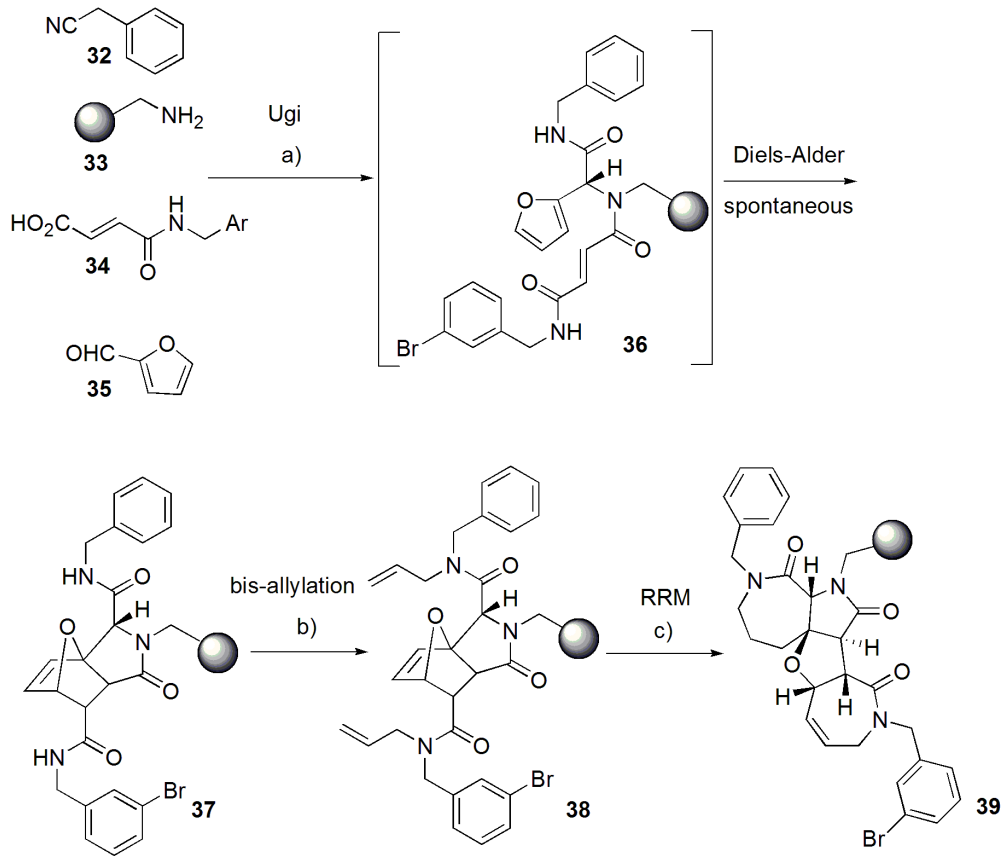
DOS requires reactions, or transformations, that promote its quest for the conversion of simple starting materials into complex products. Many multicomponent reactions are suitable for this purpose, including the asymmetric [3+2] azomethane ylide cycloaddition,[29] and the Cu(II)-pybox catalysed Passerini reaction,[30] both illustrated in **Scheme 1.4**. Both reactions proceed in excellent yield and in a highly stereoselective manner, generating complex products in just one step from relatively simple starting materials.




**Scheme 1.4** *Highly stereoselective complexity-generating reactions.*[29,30]

**A**: Asymmetric [3+2] azomethine ylide cycloaddition. **B**: Three-component Passerini reaction.

Further complexity can be introduced by the identification of pairwise-relationships, where the product of one reaction is the substrate for another. These offer enormous potential for the generation of increasingly complex skeletons.[14] This was shown in an Ugi/Diels-Alder/ring-rearrangement metathesis sequence to the synthesis of complex polycycle **39** in just three steps (**Scheme 1.5**).[31]




**Scheme 1.5** *Three-step synthesis of a complex polycyclic 7-5-5-7 ring system.*[31]

a) MeOH, THF, 48 h, 67%; b) KHMDS, allyl bromide, r.t., 18 h, 69%; c) Grubbs II, $CH_2Cl_2$, 40 °C, 36 h, 69%.

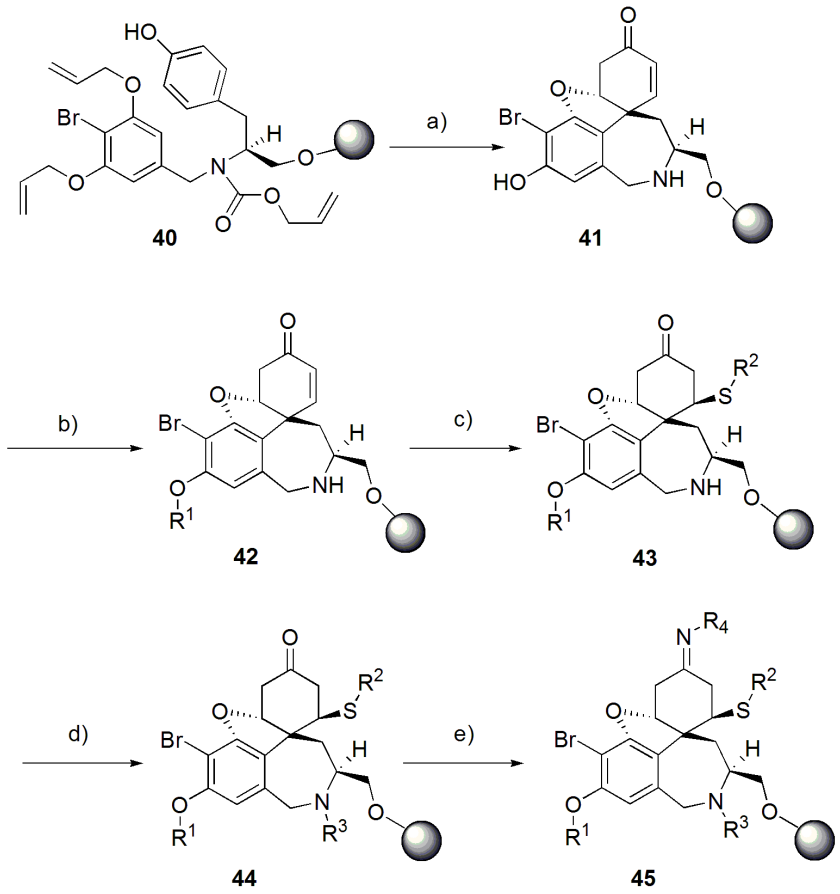
Careful choice and combination of transformations can therefore be a very powerful method for developing complex products in very few steps. Numerous examples of these types of reactions, and others, have been reported in the synthesis of DOS libraries.[32-34]

### 1.5.3 Diversity-generating processes (similar → diverse)

In order to populate large areas of chemical space efficiently, DOS aims to move in the direction of similar structures to diverse structures. In order to do this, a series of products-equals-substrates relationships must be planned, where the products of one diversity-generating reaction share some common reactive functionality suitable for another reaction.[14] Three different types of diversity can be identified in realising the goals of DOS, namely appendage (or building-block), stereochemical and skeletal diversity.

### 1.5.3.1 Appendage diversity

Combinatorial chemistry uses coupling reactions in conjunction with split-pool chemistry, to attach different building blocks to a molecular skeleton.[7] In forward-synthetic analysis these are referred to as appending processes and tend to be performed using more sophisticated organic transformations than standard combinatorial synthesis. Multiple appending processes can be used on a common molecular skeleton to huge success, resulting in libraries of hundreds, thousands or even millions of members.[35] One such example is illustrated in **Scheme 1.6**, where acyclic precursor **40** undergoes oxidative cyclisation to rigid skeleton **41**, followed by four separate appending processes.[36]



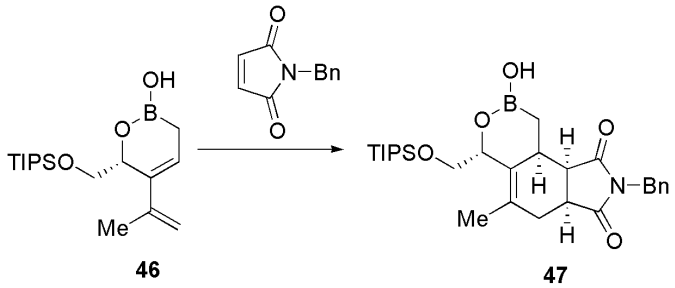

**Scheme 1.6** *Appending processes for the elaboration of a molecular skeleton.*[36]

a) i) $PhI(OAc)_2$, $(CF_3)_2CHOH$, $CH_2Cl_2$, 23 °C; ii) $Pd(PPh_3)_4$, morpholine-THF, 23 °C; b) $R^1OH$, $PPh_3$, DIAD, THF, 0 °C; c) i) $R^2SH$, 2,6-lutidine; ii) *n*BuLi, THF 0 → 40 °C; d) $R^3CHO$, AcOH, MeOH-THF, then $NaBH_3CN$ in MeOH, 23 °C or $R^3COCl$, 2,6-lutidine, $CH_2Cl_2$, 23 °C or $R^3NCO$, $CH_2Cl_2$, 23 °C; e) $R^4NH_2$, AcOH, MeOH-$CH_2Cl_2$, 23 °C.

These processes encompass a Mitsunobu reaction to couple $R^1$; conjugate addition of thiols ($R^2$) to the cyclic enone; condensation or alkylation of the nucleophilic secondary amine to couple $R^3$; and finally reaction of the electrophilic ketone with hydroxylamines or hydrazines to couple $R^4$. As a result a library of 2527 molecules was submitted for biological screening, resulting in the identification of a novel compound that blocks protein transport from the Golgi apparatus to the cell membrane.[36]

### 1.5.3.2 Stereochemical diversity

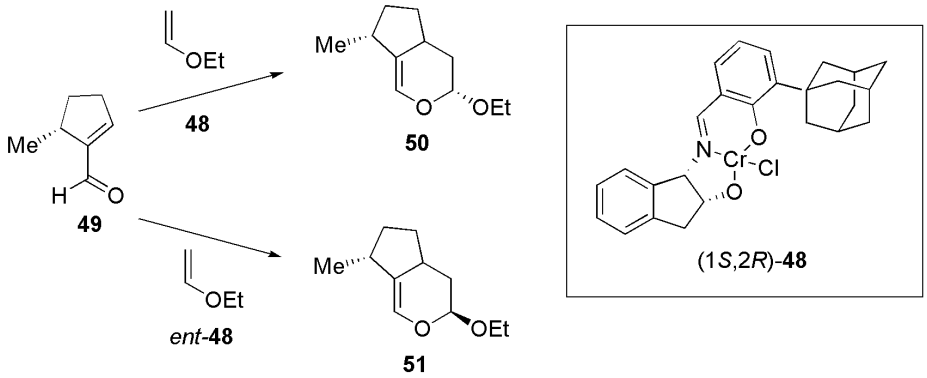
The incorporation of stereochemical diversity is essential to DOS-library synthesis in order that the orientations of macromolecule-interacting elements are maximised. This requires the use of enantio- or diastereoselective reactions that are also general, since they must be amenable to a collection of substrates.[14] One such example is the diastereoselective intermolecular Diels-Alder transformation of chiral dialkenylboronic acid **46** into cycloadduct **47**, with the selective formation of three stereocentres (**Scheme 1.7**).[37] In this example, steric interactions with the TIPS-protected hydroxymethyl group direct cycloaddition to the less hindered face of the diene, giving rise to only one stereoisomer.




**Scheme 1.7** *Stereoselective Diels-Alder reaction of a chiral dialkenylboronic acid.*[37]

Although highly stereoselective reactions may increase the overall yields of DOS processes, they do have a disadvantage in that they limit the potential synthesis of the other possible stereoisomer products. In a situation where maximum diversity is required, the potential to tune particular reaction conditions in order to obtain any stereoisomer of choice, would prove highly useful.

For example, chiral catalyst **48** can be used in a hetero-Diels-Alder reaction to overcome the stereochemical bias of a chiral substrate **49** and generate diastereomeric products with high selectivity. (**Scheme 1.8**)[14,38] The (1*S*,2*R*) catalyst shown leads to the formation of product **50**, however selective use of the enantiomer of catalyst **48** leads to the formation of the diastereomeric product **51**. The discovery of powerful reagents that are able to override stereochemical bias are essential to the further development of stereochemical diversity in DOS.




**Scheme 1.8** *The use of a chiral reagent to override the stereochemical bias of a chiral substrate.*[14,38]

### 1.5.3.3 Skeletal diversity

The introduction of skeletal diversity to a small molecule library can be achieved using either a reagent–based approach (**Figure 1.12**, **A**), or a substrate-based approach (**Figure 1.12**, **B**).[3] Reagent-based approaches encompass the use of a *pluripotent functionality*, where the same part of the molecule is subjected to different transformations induced by different reagents; or, the use of a *multiple-group pairing* strategy where different parts of the same densely functionalised molecule, are transformed by different reagents. Alternatively, a substrate-based approach called a *folding process* can be used, where different structurally encoding elements (σ elements), contained in different substrates, are subjected to the same reaction conditions.

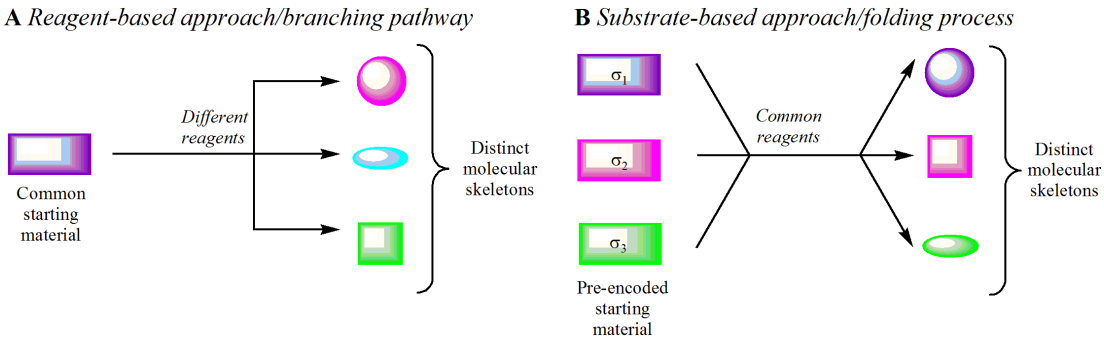
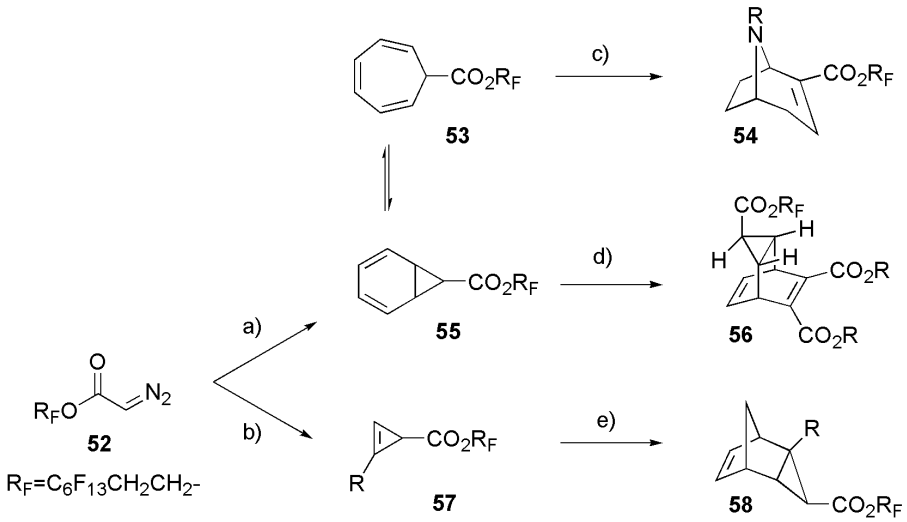



**Figure 1.12** *Generalised methods for achieving skeletal diversity.*[3]

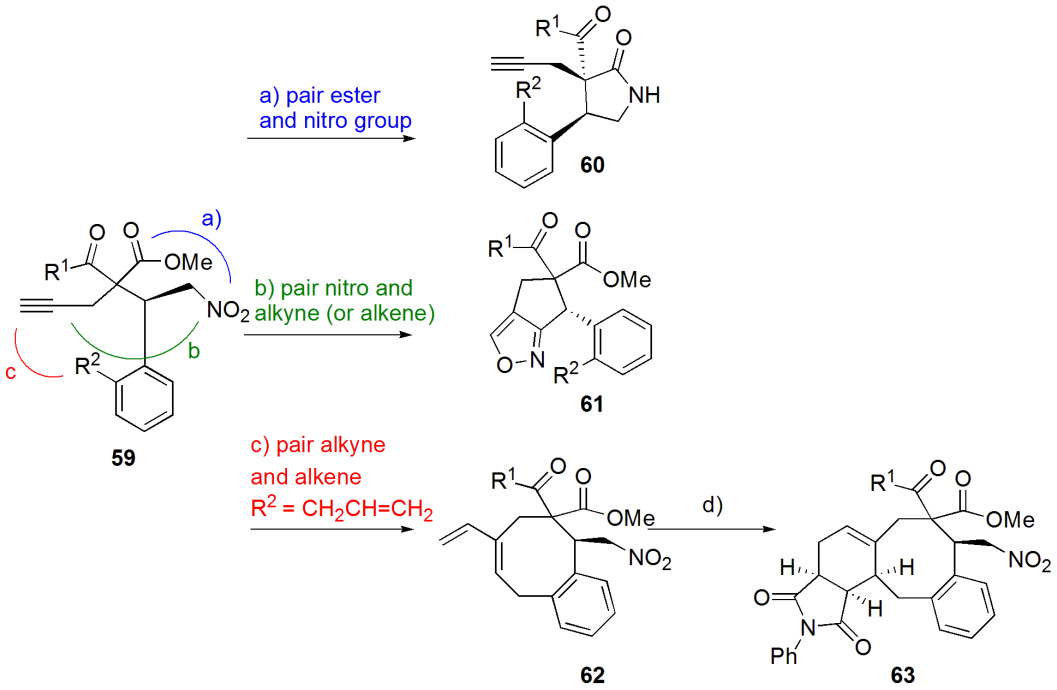
An example of achieving skeletal diversity through the use of *pluripotent functionality* is illustrated in **Scheme 1.9**, using polyfluorocarbon tagged diazoacetate **52**.[39] The fluorous tag enables the use of various purification technologies, making the methodology compatible with high-throughput solution-phase combinatorial chemistry. The diazoacetate was utilised in various divergent reactions to give a wide variety of molecular skeletons including **54**, **56** and **58**. A small molecule collection of 223 compounds was synthesized in total, and found to occupy a greater area of chemical space than a focused library, or small pharmacological library, when assessed using molecular descriptors and PCA.




**Scheme 1.9** *Pluripotent functional group strategy using a fluorous-tagged diazoacetate.*[39]

a) $C_6H_6$, $Rh_2(O_2CCF_3)_4$, 70%; b) RC≡CH, $Rh_2(OAc)_4$, [BuC≡CH, 57%]; c) $RNH_2$, NaOH then MeOH, $H_2SO_4$, [$MeNH_2$, 35%]; d) dienophile [dimethyl acetylenedicarboxylate, 59%]; e) $C_5H_6$, 92%.

*Multiple-group pairing* strategies make use of densely functionalised molecules with pendant functionality. Different pairings of pendant functionalities give rise to multiple scaffolds using different reagents.[3] For example, pairing the nitro and ester functionality of substrate **59** gives rise to lactam **60** under reductive cyclisation conditions (**Scheme 1.10**).[40] Alternatively the nitro functionality of **59** could be activated towards reaction with the alkyne through intramolecular 1,3-cycloaddition of the derived nitrile-oxide, to afford bicyclic isoxazole **61**. Finally, the alkyne could be subjected to microwave-promoted enyne metathesis conditions to afford diene **62**, suitable for further elaboration under Diels-Alder conditions.




**Scheme 1.10** *Multiple-group pairing approach to skeletal diversity.*[40]

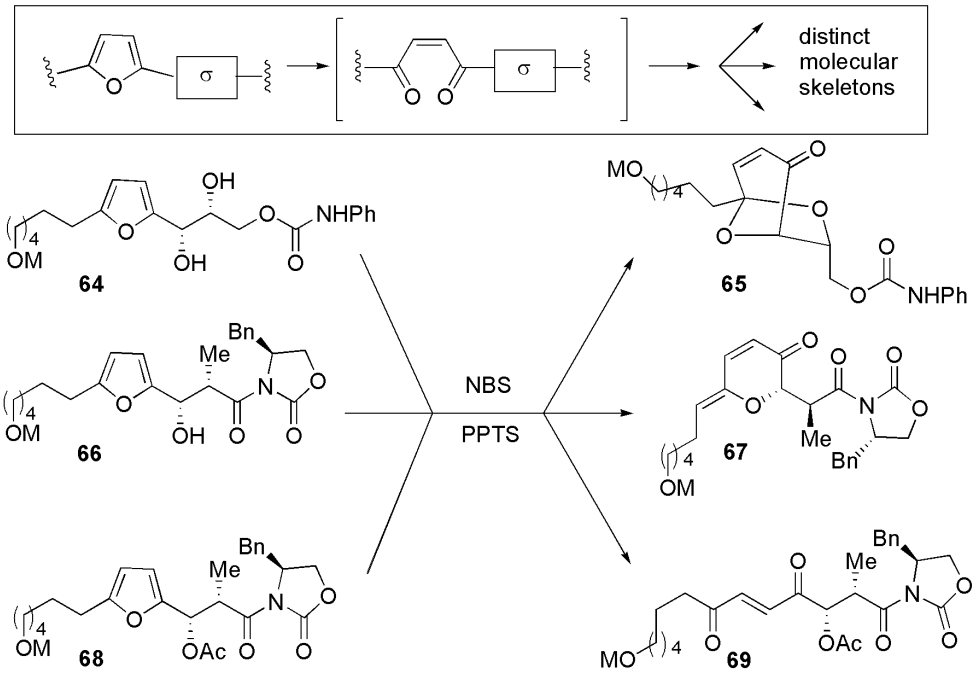
a) i) Zn, AcOH/THF; ii) $Na_2CO_3$ (aq), 92%; b) PhNCO, $Et_3N$, PhMe, r.t., 74%; c) Grubbs I, ethylene, μwave (150 W), 60 °C, $CH_2Cl_2$; d) *N*-phenylmaleamide, μwave (300 W), 160 °C, PhMe, 98%, 2 steps.

The *folding process* approach to DOS library synthesis makes use of substrates containing pre-encoded skeletal information (σ elements) that can be transformed into distinct molecular skeletons using common reaction conditions.[14] Folding processes present a useful way to introduce new skeletons towards the end of a synthesis, whilst also enabling the generation of skeletons that might otherwise be difficult to access. Folding processes are also highly amenable to split-pool solid

phase synthesis, as a result of the structural similarity and therefore common reactivity, that is present until a later stage in the synthesis.

To plan such folding processes, a relatively unreactive core structure must first be identified, that can be transformed into a more reactive intermediate upon treatment with mild reagents.[14] Various pre-encoded appendages (σ elements) having complementary reactivity to the reactive intermediate can then be attached to the common core. Finally, mild conditions are used to liberate the reactive intermediate, trigger reaction with the σ elements, and generate the different skeletons.

One such example of a relatively unreactive core is the aromatic furan ring that, upon treatment with a mild oxidant, can liberate a highly reactive *cis*-enedione intermediate (**Scheme 1.11**).[14,41] By the appendage of three distinct two-carbon chains containing zero, one, or two hydroxyl groups to the furan core, it was possible to transform three similar substrates into three skeletally diverse products, using oxidative (NBS) then acidic (PPTS) conditions. Product **65** was formed via an oxidative ring opening followed by olefin isomerisation.[42] Bicyclic ketal **67** was formed via NBS-mediated oxidative ring expansion followed by subsequent ketalisation.[43] Finally, following oxidative ring expansion, substrate **68** underwent acid-catalysed dehydration to afford pyran-3-one **69**.




**Scheme 1.11** *A skeletal diversity-generating folding process.*[14]

M = macrobead.

### 1.5.4 Summary of DOS

Although the logic of DOS is still evolving, the information described above illustrates the clear guidelines and principles that are in place to promote its further development. The libraries that have been created so far using these principles of appendage, stereochemical, and skeletal diversity have shown great promise in both biological screens and PCA analysis, providing validation for the approach as a method for bioactive small molecule discovery.

An alternative approach to small molecule library synthesis is known as biologically oriented synthesis (BIOS).[6] While DOS centres on libraries that are structurally diverse and complex, BIOS centres on libraries based around scaffolds of proven biological relevance. Although these approaches are conceptually different, they are not mutually exclusive since DOS libraries can be based around biologically privileged structures and BIOS libraries can be derived from hits generated in DOS campaigns. BIOS also significantly overlaps with the principles behind natural product libraries, however there are important differences that will be discussed below.

## 1.6 Biologically oriented synthesis (BIOS)

BIOS relies on principles derived from matching the complementary properties of bioactive small molecules, with their protein targets. If nature only explored a tiny amount of chemical space during evolution then it makes sense that there are huge untapped areas where great bioactivity may be discovered (this has been discussed previously, see **section 1.3**). The same is true for protein structures, nature only made use of a tiny fraction of all the possible amino acid combinations during evolution.[6] Additionally, the three-dimensional folds of protein structures are highly conserved in structure, since similar fold structures can be formed by different amino acid sequences.

As a result of this, BIOS forges both natural products and proteins in its approach to library synthesis. Only scaffolds of proven biological relevance are chosen as starting points for library design, and the libraries generated are small, focused and limited in diversity. BIOS uses two concepts to aid its development, the scaffold tree (discussed previously, **section 1.4.2**) and protein structure similarity clustering (PSSC).[6]

### 1.6.1 Protein structure similarity clustering (PSSC)

Proteins are built up from one or more domains that can be classified by their fold types (the spatial arrangement of secondary structure elements such as α-helices and β-sheets). It is estimated that the majority of proteins are built up from only 1000 fold types, although between 1000 and 10,000 different folds should exist in nature.[6] As a consequence of this, and the limited number of natural product scaffolds, the prediction of small molecule scaffolds that might target whole groups of structurally similar proteins may be a feasible task (**Figure 1.13**).

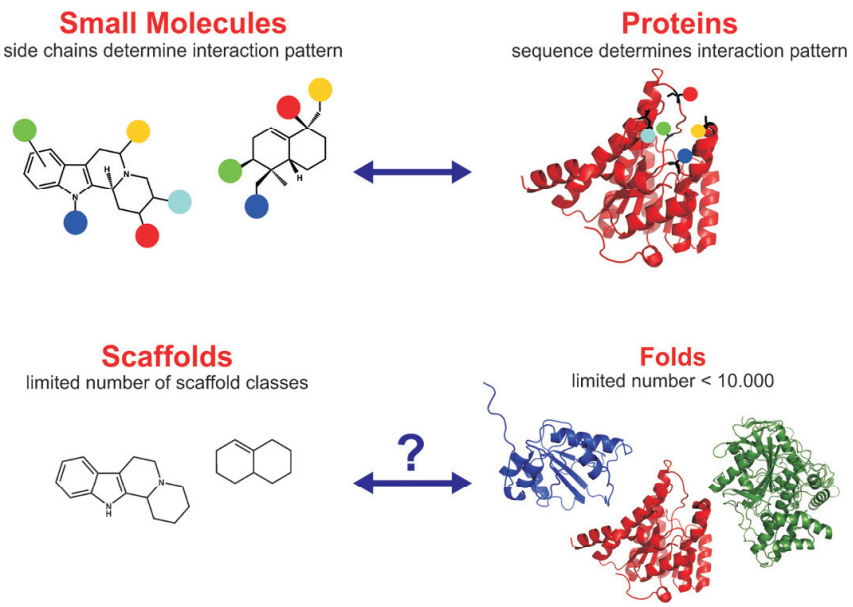



**Figure 1.13** *The principles of BIOS.*[6]

Complementary binding between small molecules and proteins may lead to the identification of a similar complementary interaction between protein folds and small molecule core scaffolds.

PSSC uses computational algorithms to identify proteins in which the fold structure around the small molecule ligand-sensing core is similar. These structures are then assigned to the same protein similarity structure cluster. If a small molecule ligand is known for one member of the cluster, then it is rational to use the scaffold as the basis for a library that might target other members of the same cluster.

### 1.6.2 PSSC and Structural classification of natural products (SCONP)

The scaffold tree (**Figure 1.6**) is a method for the structural simplification of complex architectures that also enables links between scaffold types to be realised. The inner segment of the scaffold tree depicts less complex scaffolds, therefore moving inward along branches of the tree leads to the structural simplification of complex scaffolds.[6] This can be used to identify suitable scaffolds for the basis of a library, following the identification of a small molecule during PSSC. This method was used to study the Cdc25A phosphatase protein cluster (**Figure 1.14**),[44] which consists of Cdc25A phosphatase, AChE and 11β-hydroxysteroid dehydrogenase (11βHBD). Glycyrrhetinic acid **70** is known to be a ligand of 11βHBD, so its pentacyclic core was deconstructed using the scaffold tree to give several simpler scaffolds. One of these scaffolds, the dehydrodecaline **71** also formed the core structure of dysidiolide **72**, whose natural receptor Cdc25A was also part of the cluster. This core structure was therefore considered to be a double-validated starting point for synthesis of a library of 11βHBD inhibitors, and indeed the resulting 500-member library produced 30 inhibitors with $IC_{50}$ values below 10 μM. This success clearly validates the principles of BIOS as a suitable approach for small molecule library design.

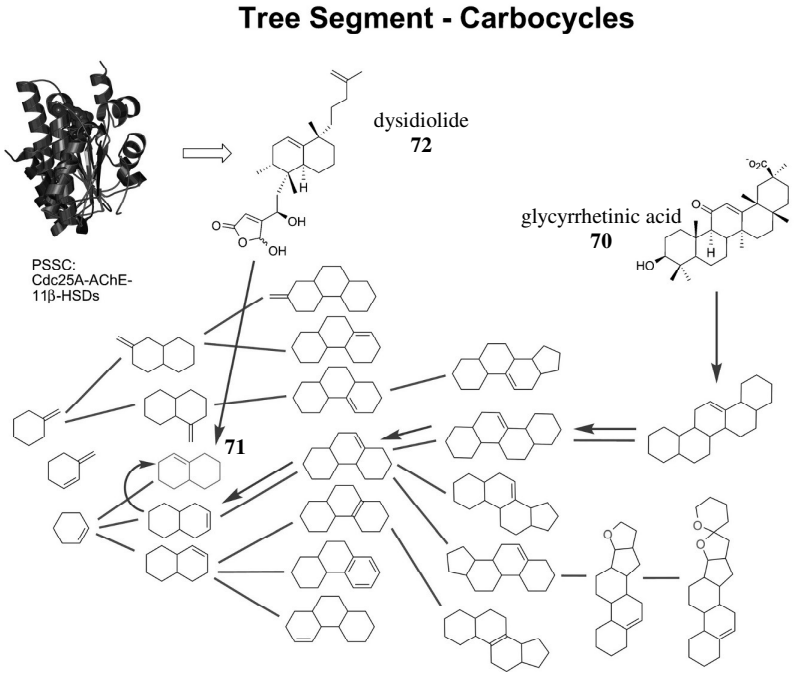



**Figure 1.14** *Merging PSSC and SCONP as a basis for library design.*[6]

## 1.7 Conclusions

Chemical genetics and drug discovery require small molecule libraries to further their development, and over the last decade or so, many approaches have been reported in the literature towards realising these demands. Many of these approaches are reliant upon solid-phase synthesis, and developments in this area have been fundamental to the advancement of library synthesis. Underpinning the majority of approaches is the use of natural products as a basis for library design. This can be in a very general sense (e.g. DOS), or more specifically (e.g. TOS, focused libraries, BIOS libraries). However, regardless of the approach that is used, the biological results clearly speak for themselves, fully justifying these methods for the successful discovery of novel bioactive small molecule ligands.

## 1.8 Proposed work

This thesis documents the work performed towards the synthesis of a small library of compounds based on the phenanthridine core **73** (**Figure 1.15**). The phenanthridine core forms an excellent basis for library design as it lies at the heart of numerous bioactive natural products including the antitumor antibiotic pancratistatin **74**;[45] antiviral lycorine **75**;[45,46] and the tubulin polymerization inhibitor chelidonine **76** (**Figure 1.15**).[47,48]

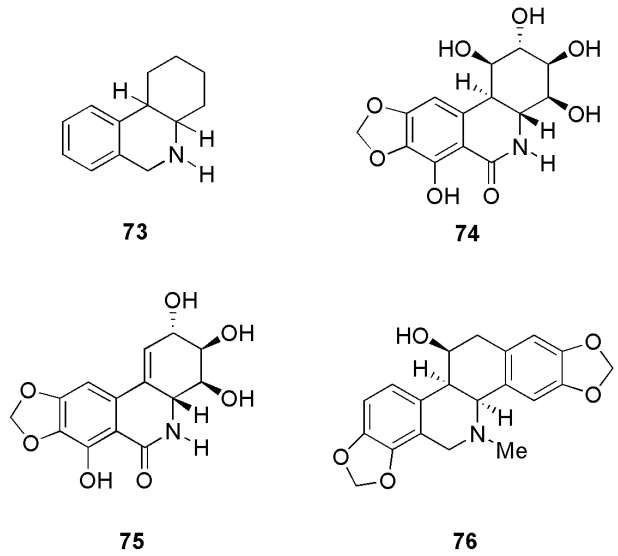



**Figure 1.15** *The phenanthridine core and bioactive-phenanthridine based natural products.*[45-48]

We decided to focus our library around the *cis*-ring fused phenanthridine core (**Figure 1.16**) as the corresponding *trans*-analogues had already received significant attention in the literature.[45,46] In realising our library, we developed novel Heck methodology for the synthesis of *cis*-ring fused phenanthridine core structures, which is described in **Chapter 2**.[49] Additionally, methodology for the further elaboration of the phenanthridine core was developed, using the principles of DOS library synthesis (skeletal, stereochemical and appendage diversity) and natural product library design (**Figure 1.16**). This work is described in **Chapter 3**.

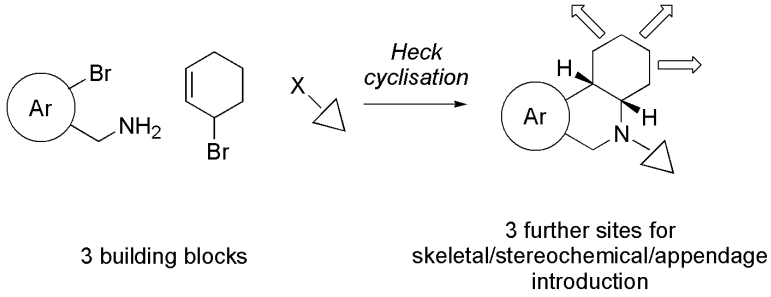


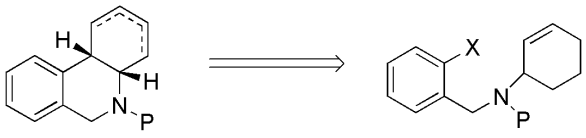

**Figure 1.16** *Phenanthridine library synthesis using the principles of DOS.*

The methodology developed in **Chapters 2** and **3** was then applied to the synthesis of a small library of phenanthridine analogues in **Chapter 4**. The biological assessment of the library was carried out using whole organism phenotype screening in zebrafish,[50] which allows the simultaneous evaluation of all possible targets resulting from the protein domain similarities highlighted by PSSC.[6]

## *RESULTS AND DISCUSSION PART 1*
## CHAPTER 2

### HECK CYCLISATION STUDIES

A survey of conditions for the palladium catalysed intramolecular Heck cyclisation of protected benzylamines **77** to afford *cis*-ring fused phenanthridines **78** was conducted to determine the optimal conditions to carry out this transformation. This survey involved a catalyst screen, application of the optimal conditions to a range of protected benzylamines and a mechanistic study to probe the double bond isomers obtained as a result of the Heck cyclisation.

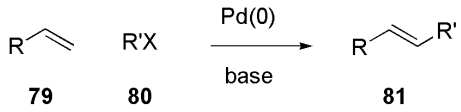



**78** **77**

**Scheme 2.1** *Heck cyclisation studied in* ***Chapter 2.***

## 2.1 The Heck reaction

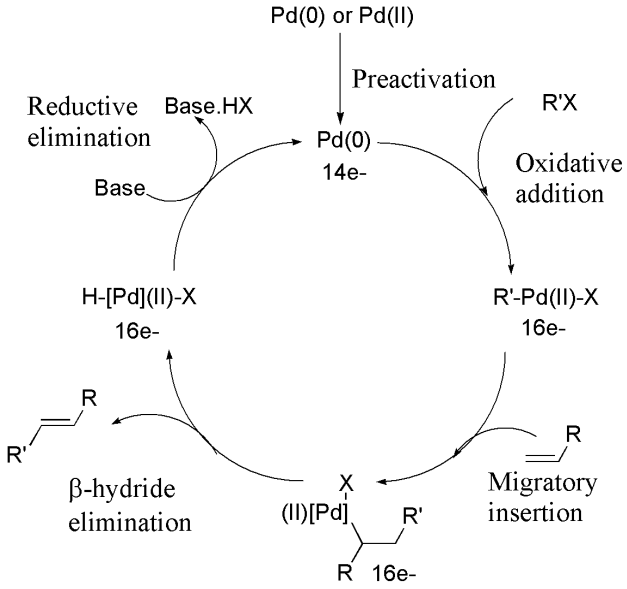
The Pd(0) catalysed vinylation of an aryl halide was reported over 30 years ago in independent studies by Mizoroki[51] and Heck.[52] The transformation is now generally referred to as the Heck reaction and is defined as the Pd(0) catalysed coupling of an aryl or vinyl halide **79** to an alkene **80** (**Scheme 2.2**).[53]




**Scheme 2.2** *The Heck reaction.*

R = H, alkyl, aryl, CN, $CO_2R$, OR, OAc, NHAc. R' = aryl, vinyl. X = I, Br, Cl, OTf.

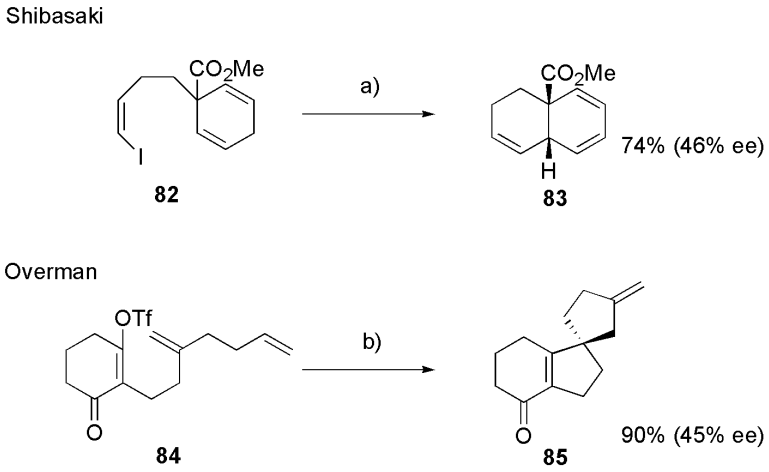
The reaction proceeds via a catalytic cycle (**Scheme 2.3**) and involves oxidative addition of the Pd(0) to the C-X bond, migratory insertion of the Pd(II) into the alkene bond, β-hydride elimination to give the coupled alkene product, followed by reductive elimination to regenerate the catalytically active Pd(0) species.




**Scheme 2.3** *Traditional mechanism of the Heck reaction.*

R, R' and X as above. Ligands omitted for simplicity.

Since its discovery, the Heck reaction has been studied intensively, furthering the development of conditions to allow a huge range of couplings to take place efficiently. The first intramolecular Heck reaction was reported in 1977, by Mori and Ban[54] and this was further developed into the asymmetric intramolecular Heck reaction, first reported independently by Shibasaki[55] and Overman in 1989.[56]




**Scheme 2.4** *First examples of an asymmetric Heck reaction.*[55,56]

a) $Pd(OAc)_2$, (*R*)-BINAP, $Ag_2CO_3$, NMP, 60 °C; b) $Pd(OAc)_2$, (*R*,*R*)-DIOP, $Et_3N$, benzene, r.t.

Shibasaki's work illustrated for the first time that an intramolecular Heck reaction could be used for the creation of a tertiary stereocentre. Overman illustrated that the intramolecular Heck reaction could be used to establish a quaternary stereocentre. Despite the modest enantioselectivities achieved with these initial examples, both studies illustrated the enormous potential of the asymmetric Heck cyclisation, and it has subsequently become the focus of many research groups worldwide and found successful application in many total syntheses.[57-59]

Another area of Heck chemistry that has received a lot of attention is the development and study of new catalyst systems for more efficient Heck couplings. Traditionally, catalysts employed in the Heck reaction have a turnover number (TON) somewhere in the region of $10^2$ – $10^3$ (loadings 1 – 5 mol%). While this is more than acceptable for application in pharmaceutical and fine chemical synthesis, it is less so for plant scale synthesis where a TON of $>10^3$ (0.1 mol% loading) is desirable. To this end, extensive research has given rise to numerous catalytic

systems able to deliver such TONs, including palladacycles, coordinatively unsaturated Pd catalysts featuring bulky phosphanes [e.g ($^t$Bu$_3$P)$_2$Pd], carbene ligands and even ligandless palladium.[60] Catalysts like ($^t$Bu$_3$P)$_2$Pd have also proved to be particularly effective for the cross coupling of aryl chlorides and for room temperature cross-couplings.[61,62]

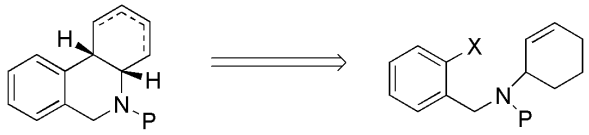
Like most organometallic cross-coupling reactions, the Heck reaction has been successfully carried out under microwave conditions.[63] This rapid method of heating allows the elevated temperatures required for reaction to be reached in seconds, and in conjunction with the pressurised, sealed reaction vessels permits successful coupling in a matter of minutes. Generally microwave mediated cross-coupling reactions are found give less side products than conventional heating methods as the whole volume of the reaction solution can be heated simultaneously and uniformly. They are seen as a greener alternative to standard heating methods with regard to the amount of electricity employed, and the volume of water that is not wasted on condenser cooling.[64]

One final area of Heck chemistry that has received much attention recently is the reaction mechanism.[65,66] The sheer wealth of catalysts, ligands and results that have been generated in this area have led to some debate as to what the exact mechanism of the Heck reaction actually is. Recent reports have made claims for Pd(II)/(IV) catalytic cycles, and indeed some Pd(IV) species have been isolated.[67,68] However generally, the standard neutral Pd(0)/Pd(II) cycle (**Scheme 2.3**) is accepted as the most accurate mechanism, although this can be diverted into the cationic manifold (see **section 2.4**) by the addition of Ag(I)[69] or Tl(I) salts.[70]

.

## 2.2 Proposed work

We were attracted to an intramolecular Heck cyclisation-based approach to the phenanthridine framework (**Scheme 2.5**) as there is good precedent for *cis*-stereocontrol in the formation of the 6,6-ring junction in related phenanthridone systems.

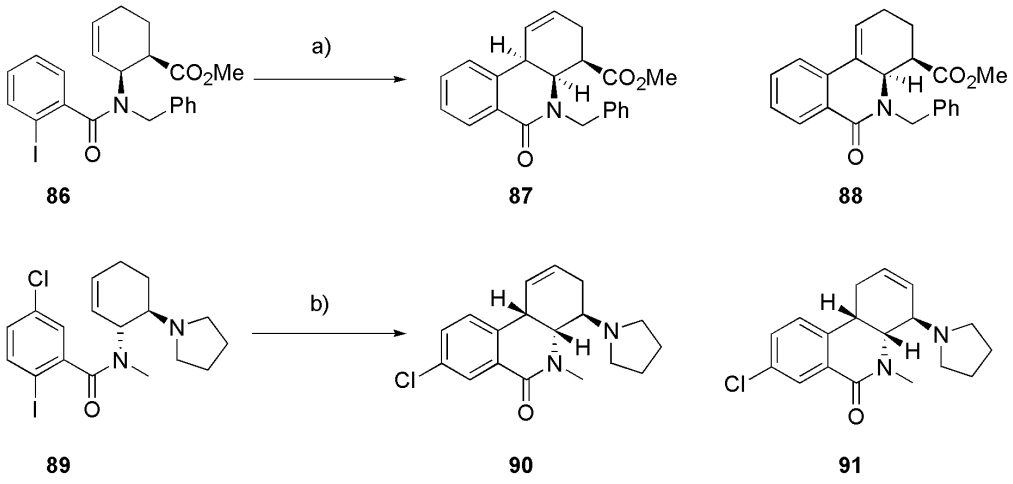



**78** **77**

**Scheme 2.5** *Phenanthridine retrosynthesis.*

P = protecting group.

For example, Grigg *et al.*[70,71] reported the successful cyclisation of aryl iodide **86** to afford predominantly the *cis*-ring fused $\Delta^{1,2}$ phenanthridone **87**, along with some of the ring junction $\Delta^{10b,1}$ double bond isomer **88**, and Szmuzkovicz[72] reported the formation of $\Delta^{1,2}$ and $\Delta^{2,3}$ *cis*-ring junction phenanthridones **90** and **91** from aryl iodide **89** (**Scheme 2.6**). The addition of $Tl_2CO_3$ permitted the reaction of **86** to be diverted into a cationic manifold and thus deliver solely *cis* $\Delta^{1,2}$ isomer **87**.




**86** **87** **88**

**89** **90** **91**

**Scheme 2.6** *Literature precedent for cis 6,6-ring junction.*[70-72]

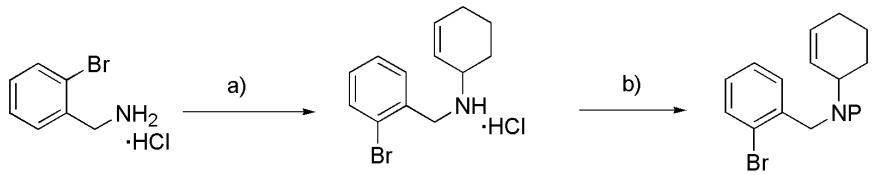
a) $Pd(OAc)_2$ (0.1 eq), $PPh_3$ (0.2 eq), $K_2CO_3$ (2 eq), MeCN, 80 °C. i) with $Et_3NCl$ (1 eq) 96 h, 78%, **87**: **88** 1.8:1. ii) with $Tl_2CO_3$, 22 h, 78% **87** only. b) $Pd(OAc)_2$ (0.1 eq), $PPh_3$ (0.2 eq), $Li_2CO_3$ (0.2 eq), DMF, 80 °C, 24 h, 72%, **90**: **91** 2:1.

Despite the literature precedent, we were concerned that the conditions reported were potentially limiting in a library-based approach to the phenanthridine core due to the lengthy reaction times (24-96 h) required for the cyclisation reaction, and the varying results with regard to the double bond isomer ratios obtained in the product.[70-74] Our initial aims were thus two-fold; to develop conditions which might overcome these practical problems, whilst at the same time promoting the cyclisation of a range of functionalised amine precursors to allow access to a diverse library based upon the phenanthridine core.

## 2.3 Catalyst screening studies

### 2.3.1 Precursor synthesis

Our first task was to synthesise suitable cyclisation precursors to test in a catalyst screen. To this end, a range of sulfonamide, carbamate and amine cyclisation precursors **94a-e** were found to be readily accessible through alkylation of commercially available 2-bromobenzylamine with 3-bromocyclohexene, followed by protection under the appropriate conditions (**Scheme 2.7**). Sulfonamide **94a** provided an excellent substrate for catalyst screening studies due to its easy purification and characterisation (no amide rotamers).




**92** **93** **94a-e**

**Scheme 2.7** *Cyclisation precursor preparation.*

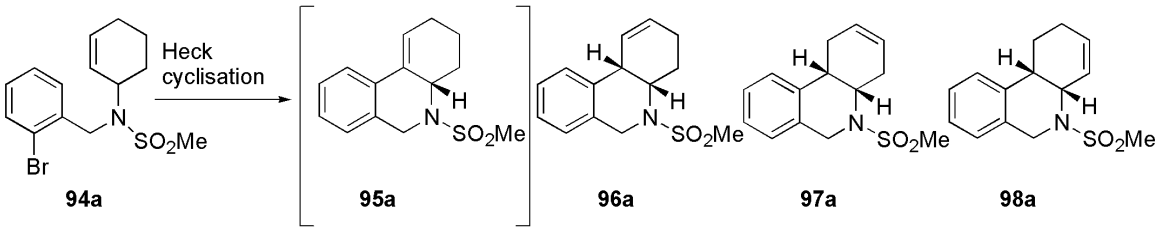
P = **94a**: $SO_2Me$; **94b** Boc; **94c** Cbz; **94d** Bn; **94e** PMB.

ai) $^{i}Pr_2NEt$, 3-bromocyclohexene, MeCN, 16 h, r.t.; aii) HCl in $Et_2O$, 99%; b) **94a** $MeSO_2Cl$, $Et_3N$, $CH_2Cl_2$, 16 h, 99%; **94b** $Boc_2O$, $Et_3N$, $CH_2Cl_2$, 16 h, 90%; **94c** NaH, DMF, 0 °C, 30 min, then benzylchloroformate, r.t., 16 h, 86%; **94d** NaH, DMF, 0 °C, 30 min, then benzyl bromide, r.t., 16 h, 81%; **94e** NaH, DMF, 0 °C, 30 min, then PMBBr, r.t., 16 h, 84%.

### 2.3.2 $Pd(OAc)_2$

We chose to use $Pd(OAc)_2$ as a starting point for our catalyst screening studies, as this was used in the corresponding phenanthridone synthesis (**Scheme 2.6**). The initial data for the $Pd(OAc)_2$ catalysed intramolecular Heck reaction of sulfonamide **94a** are given in **Table 2.1**. In related intramolecular Heck cyclisation reactions of benzamides, a range of double bond isomers have been reported, including the bridgehead $\Delta^{10b,1}$ (**95a**), $\Delta^{1,2}$ (**96a**) and $\Delta^{2,3}$ (**97a**).[72-74] In this study, none of the bridgehead double bond isomer was formed, and the *cis* $\Delta^{1,2}$ isomer (**96a**) was observed as the major product, along with trace amounts of the *cis* $\Delta^{2,3}$ (**97a**) and *cis* $\Delta^{3,4}$ (**98a**) double bond isomers.[ϕ]

**Table 2.1** *$Pd(OAc)_2$ screening for the intramolecular Heck cyclisation of sulfonamide **94a**.*




| Entry | Catalyst[a] | Base | T (°C) | t (min) | Solvent | Conversion (%)[b] | Ratio **96a:97a:98a** |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2/PCy_3$ | $MeNCy_2$ (4 eq) | 130 | 70 | DMA | 99 | 77:14:9 |
| 2 | $Pd(OAc)_2/PCy_3$ | $MeNCy_2$ (4 eq) | 140 | 60 | DMA | 99 | 96:2:2 |
| 3 | $Pd(OAc)_2/PCy_3$ | $MeNCy_2$ (4 eq) | 150 | 30 | DMA | 98 | 95:3:2 |
| 4 | $Pd(OAc)_2/PCy_3$ | $Et_3N$ (4 eq) | 140 | 70 | DMA | 58 | 90:2:8 |
| 5 | $Pd(OAc)_2/PCy_3$ | $^iPr_2NEt$ (4 eq) | 140 | 35 | DMA | 98 | 92:5:3 |
| 6 | $Pd(OAc)_2/PCy_3$ | $K_2CO_3$ (4 eq) | 140 | 40 | DMA | 87 | 55:27:18 |
| 7 | $Pd(OAc)_2/PCy_3$ | 2,6-lutidine (4 eq) | 140 | - | DMA | - | - |
| 8 | $Pd(OAc)_2/PCy_3$ | $MeNCy_2$ (4 eq) | 140 | 35 | DMF | 95 | 94:5:1 |

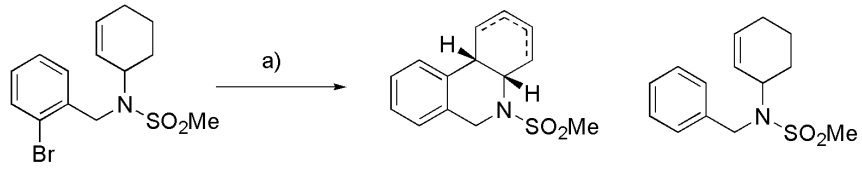
[a] [5 mol% Pd(0) source] / [10 mol% ligand] [b] Conversion was determined through analysis of the $^1H$ NMR of the crude reaction mixture.

Investigation of a range of bases at the optimum reaction temperature (140 °C) showed that $^iPr_2NEt$ gave comparable results to those obtained in presence of $MeNCy_2$, however $Et_3N$, $K_2CO_3$ and 2,6-lutidine gave lower conversion levels

[ϕ] Unequivocal confirmation of the *cis* ring junction stereochemistry and the identity of the three double bond isomer products, is reported in **section 2.5**.

(entries **4**-**7**). We observed that a switch in solvent from DMA to DMF (entry **8**) resulted in similar or even enhanced reactivity with almost total conversion in only 35 minutes.

Unfortunately however, the results in **Table 2.1** do not disclose the truth behind the reliability of our reaction. We discovered that regardless of the solvent, base or indeed the temperature (130-150 $^{o}$C) employed, two apparently identical reactions, executed side by side, exhibited different colours (yellow *vs* black) and afforded contrasting product yields and ratios. In the reactions where the solution turned black, we either observed a significant amount (>50 %) of benzylamine **99a** (**Scheme 2.8**) in addition to the desired cyclised products **96a**-**98a**, or very little reaction at all. The presence of **99a** was confirmed by comparison of the $^{1}$H and $^{13}$C NMR data of an authentic sample, synthesised in a similar manner to its bromide counterpart.




**94a** **96a-98a** **99a**

**Scheme 2.8** *Formation of benzylamine **99a**.*

a) $Pd(OAc)_2$, $MeNCy_2$, DMA, 160 $^{o}$C, 16 h, 99% **96a-98a**: **99a** 1:3.

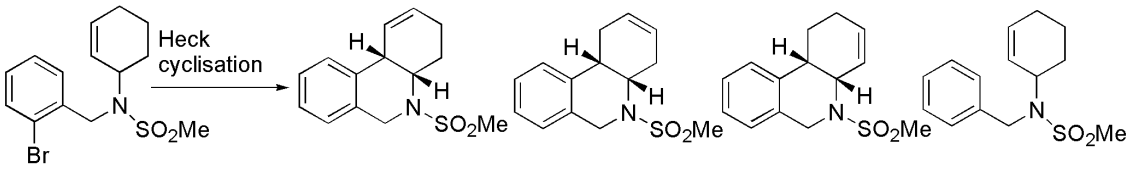
### 2.3.3 Microwave studies

As previously mentioned, microwave heating has been shown to accelerate many Pd-mediated cross-coupling reactions and can be effective at suppressing the formation of unwanted by-products, providing a generally cleaner reaction than traditional heating methods.[64] We initially had concerns that the formation of unwanted benzylamine by-product **99a** was occurring during the initial heating period (r.t.-140 $^{o}$C) and we were interested to observe whether the rapid heating period utilised in microwave synthesis (typically <30 seconds) would eliminate this unwanted product.

Initial studies showed that a temperature of 180 $^{o}$C was required to promote the $Pd(OAc)_2$ catalysed cyclisation. Performing the reaction in DMF, using either $MeNCy_2$ or $^{i}Pr_2NEt$ led to significant amounts of benzylamine **99a** being obtained (**Table 2.2**). However, using DMA as the solvent led to a significant reduction in this

unwanted by-product, with $\Delta^{1,2}$ isomer **96a** being observed as the exclusive cyclised product (entries **3**+**4**).

**Table 2.2** *Microwave accelerated intramolecular Heck cyclisation of sulfonamide* ***94a***.[a]




**94a** **96a** **97a** **98a** **99a**

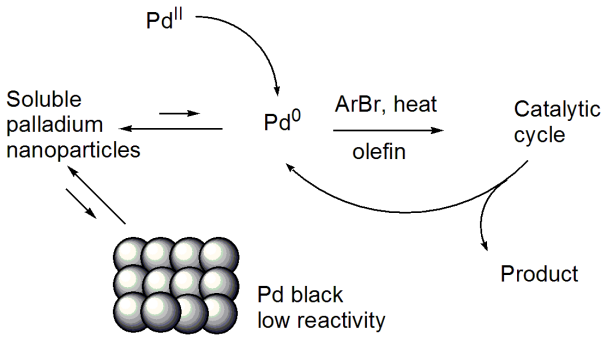
| Entry | Base | T (°C) | t (min) | Solvent | Conversion[b] (%)[b] | Ratio **96a:97a:98a:99a** |
|---|---|---|---|---|---|---|
| **1** | $MeNCy_2$ (4 eq) | 180 | 30 | DMF | 100 | 57:0:0:43 |
| **2** | $^iPr_2NEt$ (4 eq) | 180 | 30 | DMF | 100 | 70:0:0:30 |
| **3** | $MeNCy_2$ (4 eq) | 180 | 30 | DMA | 100 | 87:0:0:13 |
| **4** | $^iPr_2NEt$ (4 eq) | 180 | 30 | DMA | 100 | 86:0:0:14 |
| **5** | $MeNCy_2$ (4 eq) | 180 | 15 | DMA | 100 | 41:0:0:59 |
| **6** | $^iPr_2NEt$ (4 eq) | 180 | 15 | DMA | 100 | 66:0:0:34 |
| **7** | $MeNCy_2$ (4 eq) | 180 | 20 | DMA | 95 | 80:10:0:10 |
| **8** | $MeNCy_2$ (4 eq) | 180 | 20 | DMA | 100 | 85:12:0:3 |

[a] [5 mol % $Pd(OAc)_2$] / [10 mol% $PCy_3$] [b] Conversion was determined through analysis of the $^1H$ NMR of the crude reaction mixture.

We investigated decreasing the reaction time to determine if this had any influence on the formation of by-product **99a**, but this gave less favourable results at 15 mins (entries **5**+**6**), and only comparable results at 20 mins, and with some loss in conversion (entry **7**) and double bond isomerism (entry **8**). Our optimal conditions therefore appeared those of entry **3** or entry **8**, however again these results did not prove to be consistently reproducible, with variable amounts of **99a** being formed. We were led to conclude that regardless of the heating induction method employed, the catalyst itself was not reliable at the elevated temperatures required for reaction, using either heating approach. A survey of the literature led us to attribute this to the formation of Pd black.[75]

### 2.3.4 Pd Black

Dehalogenated benzylamines such as **99a** have been reported to form on the surface of Pd black, a colloidal species that is known to result from an excess of Pd(0) in the reaction medium (**Scheme 2.9**).[76,77] In the Heck reaction of aryl bromides and chlorides the rate-determining step is the oxidative addition, which can result in a build up of Pd(0) in solution. Further Pd(0) build up can also occur when electron rich aryl substrates which are by nature less reactive toward oxidative addition, are employed. Additionally, it is plausible to propose that a catalyst that is rapidly converted from Pd(II) to Pd(0) can also lead to a build up of Pd(0) in the reaction medium. As a consequence, the formation of soluble nanoparticles of Pd(0) is highly likely, and if these grow beyond a certain size the formation of insoluble palladium black is observed (**Scheme 2.9**) giving the reaction a black colour and leading to catalyst deactivation and the formation of dehalogenated products such as **99a**.[75]

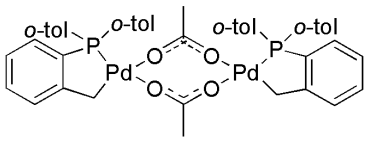



**Scheme 2.9** *Pd black formation.*[75]

It should be noted that the formation of Pd black is thought to be the eventual deactivation pathway for all standard Pd catalysed reactions,[75] but that in some cases such as ours, a combination of the elevated temperature, catalyst and substrate can lead to an acceleration of this decomposition mechanism. The capricious nature of this particular catalyst system under both standard and microwave heating, led us to investigate other possible palladium sources.

### 2.3.5 Herrmann-Beller Palladacycle

We decided to examine the Herrmann-Beller palladacycle (**100**, **Figure. 2.1**) as it is well known as a highly effective and stable source of Pd(0) for the arylation of alkenes at elevated temperatures.[78] Its use also has precedent in intramolecular cyclisation reactions.[79]



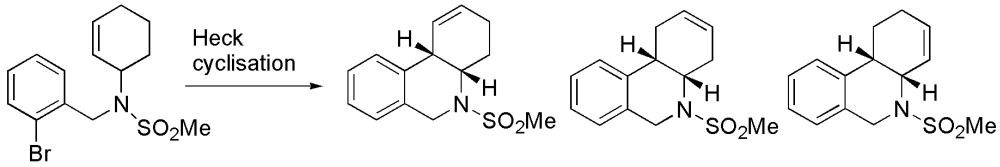

**100**

**Figure 2.1** *Herrmann-Beller palladacycle.*

The reactivity of palladacycles is often attributed to high thermal stability, resulting in a slow-releasing source of Pd(0) and thus suppression of unwanted deactivation processes.[80] While it is true that palladacycles are very thermally stable in the solid state, in solution they have actually been shown to be highly labile, undergoing facile transformations with and without fission of the palladacycle ring. Their ability to act as slow releasing reservoirs of Pd(0) is postulated to arise from their slow reaction with the other components of the reaction mixture, resulting in heterolytic cleavage of the Pd-C bond with subsequent reduction to Pd(0).[81]

The application of **100** in conjunction with the $MeNCy_2$ (the optimum base from our $Pd(OAc)_2$ studies), gave relatively rapid cyclisation at a range of temperatures (130-150 °C), but led to diminished selectivity for the $\Delta^{1,2}$ double bond isomer (**Table 2.3**, entries **1-3**).

**Table 2.3** *Herrmann-Beller palladacycle screening for the intramolecular Heck cyclisation of sulfonamide* ***94a***.




**94a** **96a** **97a** **98a**

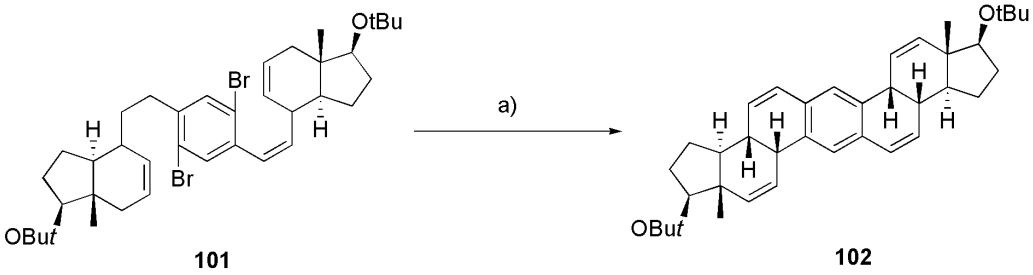
| Entry | Catalyst[a] | Base | T (°C) | t (min) | Solvent | Conversion (%)[b] | Ratio **96a:97a:98a** |
|---|---|---|---|---|---|---|---|
| **1** | Palladacycle **100** | $MeNCy_2$ (4 eq) | 130 | 360 | DMF | 85 | 39:38:23 |
| **2** | Palladacycle **100** | $MeNCy_2$ (4 eq) | 140 | 180 | DMF | 98 | 44:31:25 |
| **3** | Palladacycle **100** | $MeNCy_2$ (4 eq) | 150 | 110 | DMF | 88 | 52:16:32 |
| **4** | Palladacycle **100** | AgF (1 eq) | 140 | 180[c] | DMF | 76 | 65:23:12 |
| **5** | Palladacycle **100** | $Ag_3PO_4$ (1 eq) | 140 | 120 | DMF | 99 | 67:18:15 |
| **6** | Palladacycle **100** | $Ag_2CO_3$ (1 eq) | 140 | 70 | DMF | 99 | 85:13:2 |

[a] [5 mol % Pd(0) source] [b] Conversion was determined through analysis of the $^1H$ NMR of the crude reaction mixture. [c] No significant change observed after 180 min, even on leaving reaction for 24 h.

With the aim of finding conditions that suppressed double bond migration through a cationic reaction pathway (see **section 2.4**),[82] we screened the use of a range of Ag(I) salts (entries **4**-**6**) as additives.[83] We were pleased to discover that the use of $Ag_2CO_3$ in conjunction with the Herrmann-Beller catalyst led to rapid conversion (70 min at 140 °C), good double bond isomer ratios and excellent reproducibility. We found that modifying the equivalents of $Ag_2CO_3$ salt used as the base made very little difference to the double bond isomer ratio or conversion, with one equivalent being optimal. The application of the optimal cationic (entry **6**) reaction conditions to cyclisation precursors **94a-e** is reported in **section 2.6**.

### 2.3.6 Jeffery conditions

Jeffery pioneered the application of the Heck reaction under aqueous conditions.[84] Most recently these conditions have been successfully applied by Tietze in a double Heck reaction using the Herrmann-Beller palladacycle to establish two *cis*-annelated ring junctions (**Scheme 2.10**) in good yield.[85]



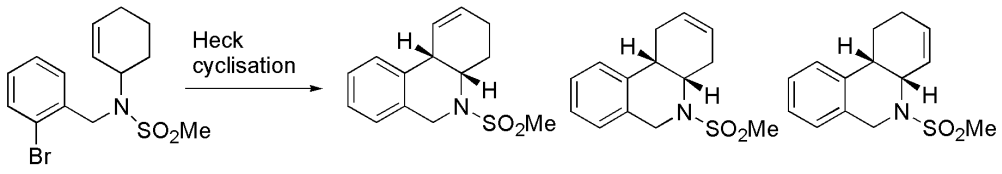

**101** **102**

**Scheme 2.10** *Application of Jeffery conditions to a double Heck reaction.*[85]

a) Palladacycle **100**, $n$Bu$_4$NOAc, DMF/CH$_3$CN/H$_2$O 1:1:0.2, 130 – 140 °C, 1.5 h, 80%.

As we had achieved success with palladacycle **100** under organic phase conditions, we applied a slightly modified version of these aqueous conditions to the cyclisation of sulfonamide **94a** (**Table 2.4**), generating the required $n$Bu$_4$NOAc *in situ* from $n$Bu$_4$NBr and KOAc.

**Table 2.4** *Application of modified Jeffery conditions to the cyclisation of sulfonamide **94a**.*




**94a** **96a** **97a** **98a**

| Entry | Conditions[a] | T (°C) | t (min) | Solvent[b] | Conversion (%)[c] | Ratio **96a:97a:98a** |
|---|---|---|---|---|---|---|
| **1** | Palladacycle **100**, KOAc, $n$Bu$_4$NBr | 140 | 120 | DMF: MeCN: H$_2$O | 100 | 49:30:21 |
| **2** | Palladacycle **100**, KOAc, $n$Bu$_4$NBr | 150 | 40 | DMF: MeCN: H$_2$O | 100 | 37:49:14 |
| **3** | Palladacycle **100**, Ag$_2$CO$_3$, $n$Bu$_4$NBr | 140 | 200 | DMF: MeCN: H$_2$O | 74 | 56:34:10 |

[a] [5 mol % Pd(0) source] [b] 1:1:0.2 ratio [c] Conversion was determined through analysis of the $^1$H NMR of the crude reaction mixture.

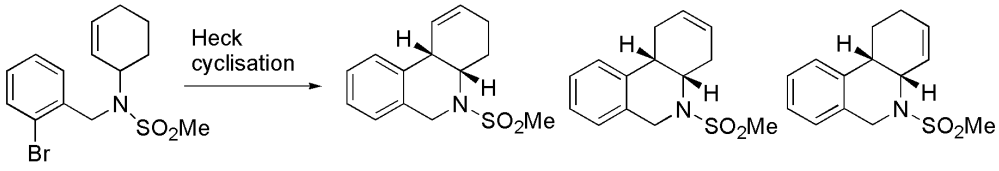
We were pleased to discover that the aqueous conditions worked well using a neutral system (KOAc/$n$Bu$_4$NBr) to give a mixture of double bond isomers. In contrast to

the normal phase neutral cyclisation conditions reported in **Table 2.3** that reach completion in 180 mins at 140 °C, these aqueous conditions take only 40 mins to give total conversion at the same temperature (entry **2**), offering a significant improvement if a mixture of double-bond isomers was desired. However when we switched KOAc for $Ag_2CO_3$ to test the reaction under conditions that favoured a cationic pathway this led to incomplete conversion (entry **3**) and a significant degree of double bond isomerism. As our initial aim was to obtain conditions for the cyclisation of sulfonamide **94a** to afford predominantly one double bond isomer product, we did not pursue these aqueous conditions any longer.

### 2.3.7 Pd(dppf)$Cl_2$

We examined the use of one further catalyst, Pd(dppf)$Cl_2$ (**Table 2.5**). While this had been reported in the literature as a successful catalyst for Pd-catalysed cross-couplings at 80 °C,[86] we found that only low conversions were obtained under both neutral and cationic conditions at this temperature (22 - 50%). In addition we had no success in obtaining complete conversion of starting material in the presence of $Ag_2CO_3$ at any temperature (entries **3**-**5**). However, complete conversion was achieved by employing Pd(dppf)$Cl_2$ under neutral conditions at 140 °C, leading to a mixture of double bond isomer products (entry **2**).

**Table 2.5** *Pd(dppf)$Cl_2$ promoted Heck cyclisation of sulfonamide* ***94a***.[a]




**94a** **96a** **97a** **98a**

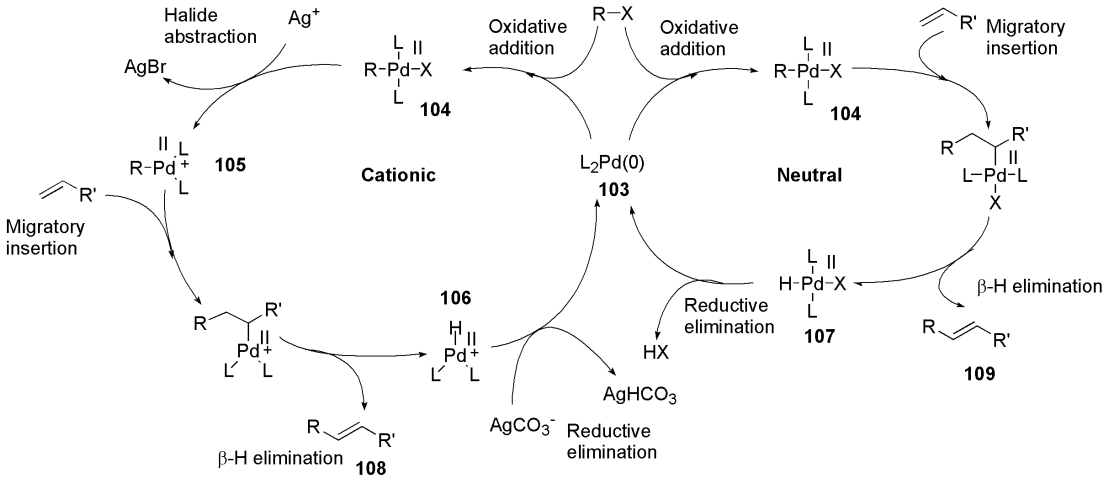
| Entry | Base | T (°C) | t (h) | Solvent | Conversion (%)[b] | Ratio **96a:97a:98a** |
|---|---|---|---|---|---|---|
| **1** | $MeNCy_2$ | 80 | 2 | DMF | 22 | - |
| **2** | $MeNCy_2$ | 140 | 2 | DMF | 100 | 37:49:14 |
| **3** | $Ag_2CO_3$ | 80 | 16 | DMF | 50 | 47:34:19 |
| **4** | $Ag_2CO_3$ | 140 | 16 | DMF | 53 | 69:21:10 |
| **5** | $Ag_2CO_3$ | 160 | 16 | DMF | 59 | 85:9:6 |

[a] [5 mol% Pd(0) source] [b] Conversion was determined through analysis of the $^1$H NMR of the crude reaction mixture.

As our optimum conditions for obtaining predominantly the $\Delta^{1,2}$ double bond isomer were obtained using palladacycle **100** under cationic conditions (**Table 2.3**, entry **6**), these conditions were taken on and applied to the range of amine and carbamate substrates in hand (see **section 2.6**).

### 2.4 Neutral vs Cationic

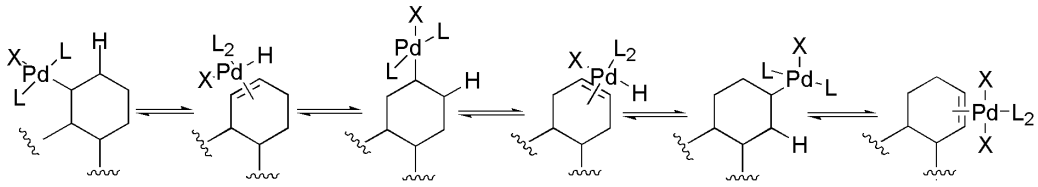
A double catalytic cycle for the Heck reaction, documenting both a neutral and a cationic Heck reaction is shown in **Scheme 2.11**. Both cycles undergo similar oxidative addition steps to afford the Pd(II) intermediate **104** as shown. In the case of the cationic pathway, the Ag(I) ion abstracts the halide from the surface of **104**, generating the cationic Pd(II) intermediate **105**. Following migratory insertion and β–hydride elimination this affords cationic intermediate **106**. It is thought this undergoes reductive elimination far faster than its neutral counterpart **107**, resulting in rapid regeneration of Pd(0) and an increased rate of reaction (**Table 2.3** entry **2** vs entry **6**).[82]




**Scheme 2.11** *The Cationic and Neutral Heck catalytic cycles.*[82]

The rapid reductive elimination step of the cationic cycle also results in decreased double bond isomerism. This is because such isomerism occurs via re-addition of the Pd(II) intermediate (**106** or **107**) to the alkene (**108** or **109**), followed by β-H elimination with an alternative proton. If the Pd(II) intermediate **106** rapidly

undergoes reductive elimination, as in the case of the cationic cycle, it is not able to participate greatly in the re-addition/β-H elimination sequence (**Scheme 2.12**), and thus double bond isomerism is reduced.

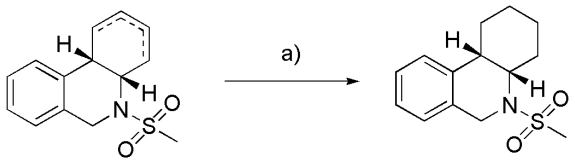


**Scheme 2.12** *Simplified illustration of double bond isomer formation (Neutral system).*

## 2.5 Product identification

### 2.5.1 Double bond isomers

The identity of **96a-98a** as double bond isomers was confirmed when a mixture of the compounds was treated under hydrogenation conditions to give a single saturated product **110** (**Scheme 2.13**). This process also told us that we had not made any of the bridgehead double bond isomer **95a**, as hydrogenation could occur at either face of this phenanthridine giving rise to both the *cis* and *trans* ring junction saturated products.




**96a-98a** **110**

**Scheme 2.13** *Double bond isomer conversion to a single product.*

a) $H_2$, Pd/C, MeOH, r.t., 16 h, 60 %.

In order to determine the structure of each double bond isomer in the product mixture, they were first separated by HPLC, followed by full characterisation using 1D and 2D NMR techniques. We initially carried out COSY and HSQC NMR spectroscopy to identify the carbon backbone of each product. The COSY then enabled us to identify the $\Delta^{2,3}$ isomer, as in keeping with its structure, this product did

not show any correlations between either of the ring junction protons and the alkene protons.

To distinguish between the $\Delta^{1,2}$ and $\Delta^{3,4}$ isomers we used 2D NOESY spectroscopy (**Figure 2.2** and **Figure 2.3**). Key correlations for identifying the $\Delta^{1,2}$ product **96a** include aromatics - alkene (Ar – a) and benzylic methylene - methylene of the cyclohexene ring - (g2 - d). In addition, the absence of the following correlations supported our structural assignment: (g – b), (h – d), (e – Ar), (d – Ar). Key correlations for identifying the $\Delta^{3,4}$ product **98a** include benzylic methylene - alkene (g2 – d) and aromatics – cyclohexene ring methylene - (Ar – a1). As above, the absence of the following correlations supported our structural assignment: (g – a), (g – b), (e – b), (d – Ar), (e – Ar).

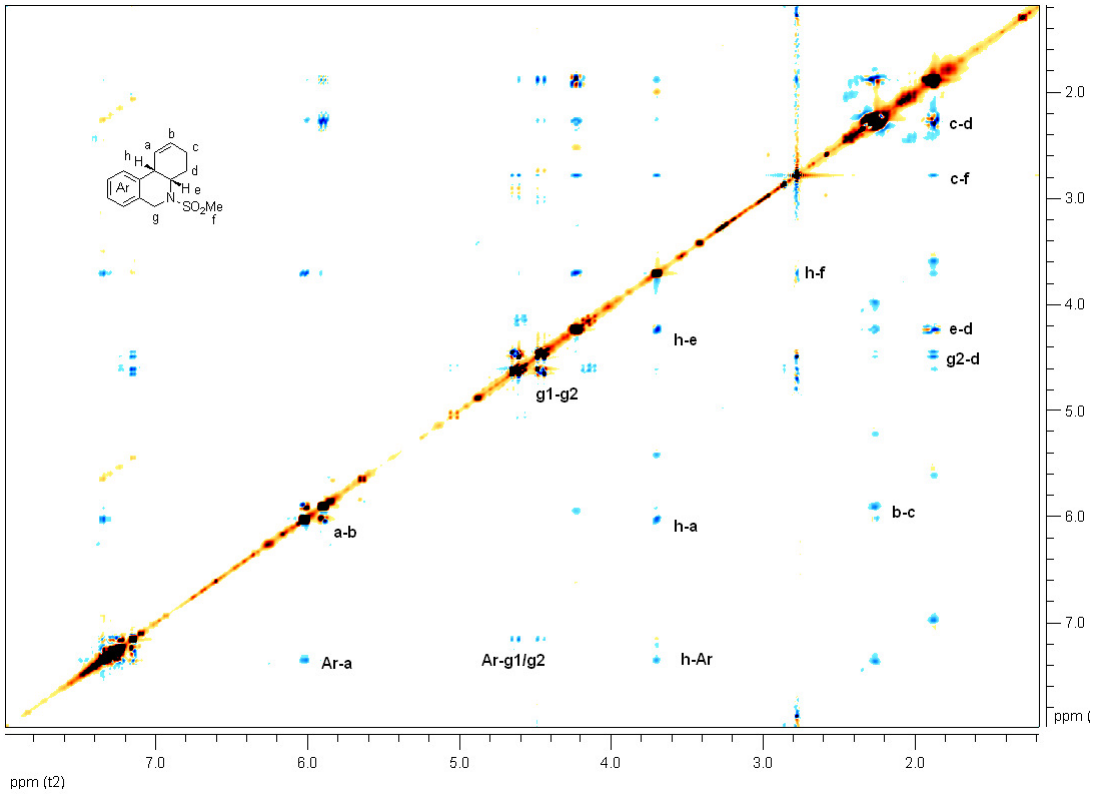



**Figure 2.2.** *2D NOESY spectrum for $\Delta^{1,2}$ isomer **96a**.*

Key correlations: (Ar – a), (g2 – d).

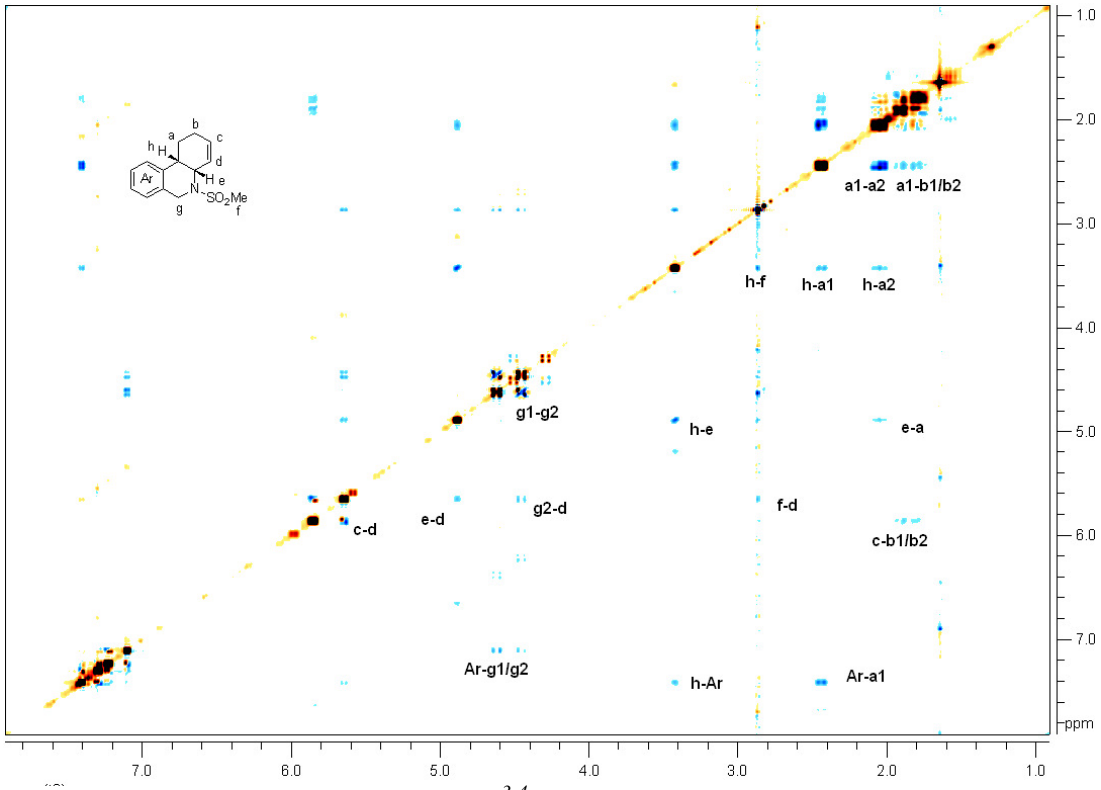



**Figure 2.3.** *2D NOESY spectrum for $\Delta^{3,4}$ isomer* ***98a***.

Key correlations: (g2 –- d), (Ar – a1).

Fortunately, each double bond isomer could be clearly identified in the $^{1}$H NMR spectrum, by the signal of its ring junction proton 'h' (**Figure 2.4**). This allowed quantification of the double bond isomer ratio for each reaction without undertaking HPLC purification.

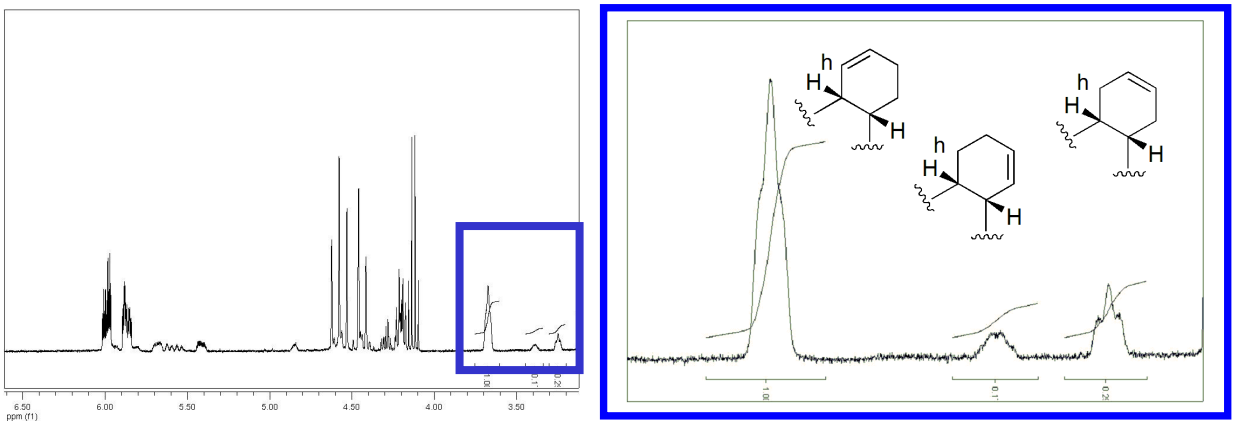
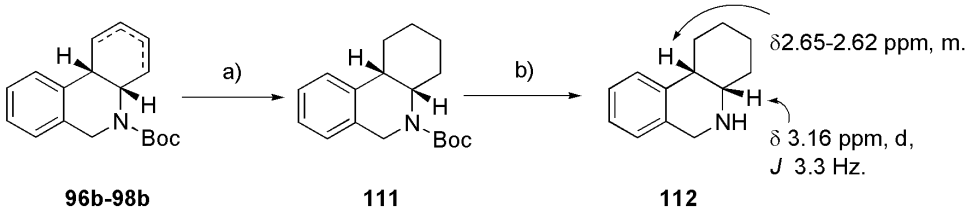


**Figure 2.4** *Double bond isomer quantification for* ***96a-98a***.

### 2.5.2 *Cis* ring junction stereochemistry

As suggested by the phenanthridone literature precedent,[70-74] Heck cyclisation of precursor **94a** gave the *cis*-ring fused phenanthridine product. Similar selectivity has also been reported for the Heck cyclisation of related carbocyclic systems.[87a] Confirmation of the *cis*-ring junction stereochemistry was gained later in this study through the conversion of a mixture of **96b-98b** to saturated phenanthridine **112** **(Scheme 2.14)**, and comparison of its $^{1}H$ and $^{13}C$ NMR data with the *cis* [δ 2.60 (1H, m) and 3.12 ppm (1H, m)] and *trans* [δ 2.36–2.49 ppm (2H, m)] ring junction phenanthridines reported in the literature.[87b] This result was in good accord with the strong nOE observed across the ring junction in all the double bond isomer phenanthridine products (**Figure 2.2** and **Figure 2.3** protons h – e).



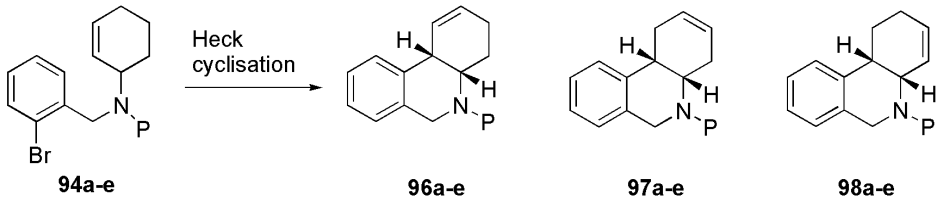

**Scheme 2.14** *Cis ring junction confirmation.*

a) $H_2$, Pd/C, MeOH, r.t., 16 h, 86%. b) TFA, $CH_2Cl_2$, 10 mins, 98%.

## 2.6 Application of cationic conditions to protected amines

Our optimal cationic conditions, reported in **section 2.3.5** were tested against our range of carbamate and amine cyclisation precursors to probe substrate scope.

**Table 2.6** *Application of optimal cationic conditions.*[a]




**94a-e** **96a-e** **97a-e** **98a-e**

| Entry | Substrate | P | t (min) | Yield (%) | Ratio (**96:97:98**) |
|---|---|---|---|---|---|
| **1** | **94a** | $SO_2Me$ | 70 | 99 | 85:13:2 |
| **2** | **94b** | Boc | 120 | 99 | 83:15:2 |
| **3** | **94c** | Cbz | 120 | 99 | 92:6:2 |
| **4** | **94d** | Bn | 120 | 92 | 100:0:0[b] |
| **5** | **94e** | PMB | 160 | 76 | 97:3:0 |

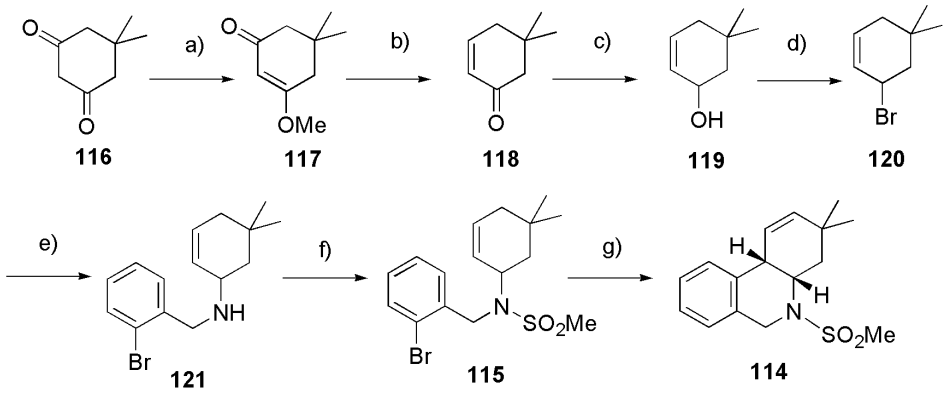
[a] Conditions: aryl halide (1 eq), palladacycle **100** (5 mol%), $Ag_2CO_3$ (1 eq), DMF, 140 °C. [b] Minor isomer peaks could not be quantified.

In all cases our optimum conditions employing the Herrmann-Beller catalyst **100** gave excellent conversions to the phenanthridine core, strongly favouring the $\Delta^{1,2}$ isomer (**Table 2.6**). With the exception of the PMB-protected amine precursor **94e**, the reactions were complete in <2 h. The Bn and PMB protected analogues in particular showed excellent selectivity for the $\Delta^{1,2}$ isomer.

The identity and ratios of the Boc and Cbz-protected products (**96b**-**98b** and **96c**-**98c** respectively) were determined by direct correlation of their $^1$H NMR spectra with their sulfonamide counterparts (**96a**-**98a**); and the assignment of minor peaks was confirmed by TOCSY experiments. For the Bn and PMB products, extensive 2D NMR analysis confirmed that the major product in each of these two cases was the $\Delta^{1,2}$ isomer (**96d** and **96e** respectively), whilst the $\Delta^{2,3}$ and $\Delta^{3,4}$ minor products, where visible, were assigned by analogy with their sulfonamide counterparts.

## 2.7 Application to a gem dimethyl analogue

In order to assess the utility of these cationic conditions on a substrate biased towards the formation of a single double bond isomer, we chose to synthesise the gem dimethyl phenanthridine analogue, **114**. The sulfonamide protected cyclisation precursor **115** was readily accessed (**Scheme 2.15**) through conversion of dimedone **116** to enol ether **117**;[88] conversion to known enone **118** via a reduction and subsequent reaarrangement on silica;[89] reduction of **118** to the corresponding enol **119** and conversion to allylic bromide **120** using $CBr_4$;[90,91] coupling of bromide **120** with 2-bromobenzylamine as described in **section 2.3.1**; and finally sulfonamide protection of the amine.




**Scheme 2.15** *Synthesis and cyclisation of gem dimethyl analogue **114**.*

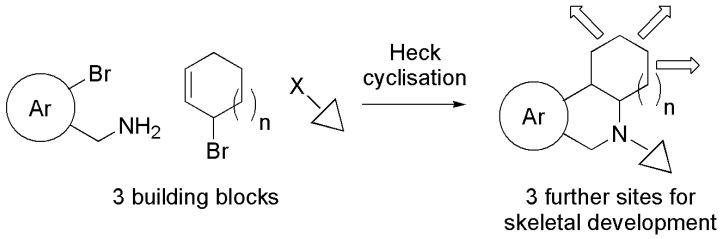
a) CAN, MeOH, r.t., 16 h, 73%; b i) $LiAlH_4$, $Et_2O$ 0 °C → r.t., 1 h; b ii) silica, $CH_2Cl_2$, 3 h, 91%; c) $LiAlH_4$, $Et_2O$, 0 °C, 40 min, 72%; d) $CBr_4$, $PPh_3$, $Et_2O$, r.t., 2 h, 67%; e) *o*-$BrPhCH_2NH_2$·HCl, $^iPr_2NEt$, MeCN, r.t., 16 h, 63%; f) $MeSO_2Cl$, $Et_3N$, $CH_2Cl_2$, r.t., 3 h, 65%; g) **100** (5 mol%), $Ag_2CO_3$, DMF, 140 °C, 2 h, 99%.

Heck cyclisation of **115** employing the Herrmann-Beller catalyst resulted in quantitative conversion in 2 h to a colourless solid which was shown to be the desired $\Delta^{1,2}$ 3,3-dimethyl-tetrahydrophenanthridine **114**. This result clearly shows the efficiency of our cationic cyclisation conditions, and illustrates their potential utility in systems with additional functionality on the cyclohexenyl ring.

## 2.8 Diversity based applications of the phenanthridine cyclisation reaction

### 2.8.1 Herrmann-Beller neutral conditions

As reported in **Chapter 1**, the synthesis of natural-product-like libraries based on strategies which make use of the rapid introduction of stereochemical, structural and skeletal diversity,[14] is one which has gained prominence in recent years as a means to efficiently cover chemical space.[6,12] The initial results obtained for the cyclisation of sulfonamide **94a** under neutral conditions in DMF or DMF:MeCN:$H_2O$ using the Hermann-Beller catalyst (**Table 2.3,** entry **2 or Table 2.4** entry **2**) offer considerable potential in this direction. In one step, the phenanthridine core unit is formed, whilst at the same time the potential for further diversification, through reaction of the newly-formed double bond at each of the three positions, $\Delta^{1,2}$, $\Delta^{2,3}$ and $\Delta^{3,4}$, is introduced. In combination with different amine precursors a large and diverse compound library based on the phenanthridine core might be rapidly assembled (**Scheme 2.16**).



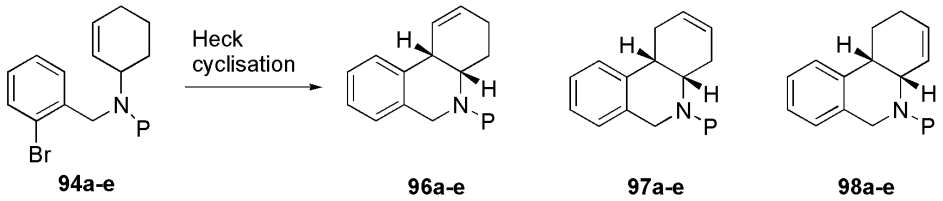

**Scheme 2.16** *Diversity oriented synthesis of a phenanthridine library.*

In order to determine the potential versatility of such an approach we screened the use of the Herrmann-Beller catalyst across the full range of precursors **94a-e** (**Table 2.7**). Although our initial result for the neutral cyclisation of sulfonamide **94a** under Jeffery conditions offered a more rapid cyclisation than that in DMF, we decided that the latter conditions had the advantage of giving a larger proportion of each isomer (37:49:14 Jeffery vs 44:31:25 in DMF) and thus used these in our screen.

We discovered that under these neutral conditions (**Table 2.7**) the Boc and Cbz protected substrates **94b** and **94c** behaved in a similar manner to **94a**, giving a double bond isomer profile suitable for diversity-based applications. The Bn and PMB protected substrates **94d** and **94e** however, gave predominantly the $\Delta^{1,2}$ isomer

rendering them unsuitable as protecting groups for the synthesis of a DOS library of phenanthridines.

**Table 2.7** *Application of neutral Herrmann-Beller conditions.*[a]




**94a-e** **96a-e** **97a-e** **98a-e**

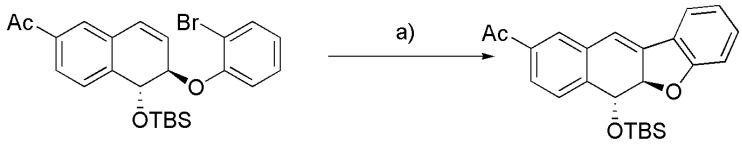
| Entry | Substrate | P | t (h) | Yield (%) | Ratio (**96:97:98**) |
|---|---|---|---|---|---|
| **1** | **94a** | $SO_2Me$ | 3h | 98 | 44:31:25 |
| **2** | **94b** | Boc | 3 h | 95 | 36:38:26 |
| **3** | **94c** | Cbz | 3 h | 99 | 33:39:28 |
| **4** | **94d** | Bn | 5 h | 93 | 83:8:9 |
| **5** | **94e** | PMB | 5 h | 93 | 74:13:13 |

[a] Conditions: aryl halide (1 eq), $MeNCy_2$ (4 eq), palladacycle **100** (5 mol%), DMF, 140 °C.

### 2.8.2 Low temperature alternative

#### 2.8.2.1 Background information

Although we were satisfied that the neutral conditions reported above would prove suitable for application in a DOS library, we examined one further catalyst system during our screening studies that offered an alternative set of low temperature conditions. As reported in **section 2.1**, the highly reactive catalyst $(^tBu_3P)_2Pd$ has been used to conduct intermolecular Heck coupling reactions at room temperature.[62] It has limited precedent in intramolecular Heck cyclisations,[92,93] with only one example of its use at low temperatures (40 °C, **Scheme 2.17**),[94] and no examples of its application in a system similar to ours, but we were keen to examine if it could offer us a low temperature set of conditions for our cyclisation.




**122** **123**

**Scheme 2.17** *Low temperature intramolecular Heck.*[94]

a) $Pd_2(dba)_3$ (1 mol%), $^tBu_3PHBF_4$ (4 mol%), DABCO (3 eq), 40 °C, dioxane, 60 h, 92%.

We were initially interested in the use of this particular catalyst system as a means of accessing predominantly the $\Delta^{1,2}$ double bond isomer. A recent literature report[95] examining the reductive elimination of HCl from $L_2PdHCl$ stated that for L = $^tBu_3P$ the process was very facile, suggesting to us that double bond isomerism might be disfavoured as in a cationic Heck reaction. Upon X-ray crystallographic analysis of the hydride species, this was attributed to the steric bulk of the ligands, (**Figure 2.5**). When compared to the corresponding $PCy_3$ hydride species, where the LL angle is 180°, it can be seen that the $^tBu_3P$ ligands are forced away from the chlorine, with an LL angle of 161° at the cost of increased steric strain between the ligands and the hydride. This strain is relieved upon reductive elimination to generate $Pd(^tBu_3P)_2$ thus providing a driving force for the process. We anticipated that an even greater relief of steric strain might be accomplished if the hydride species contained a bromine atom rather than a chlorine.

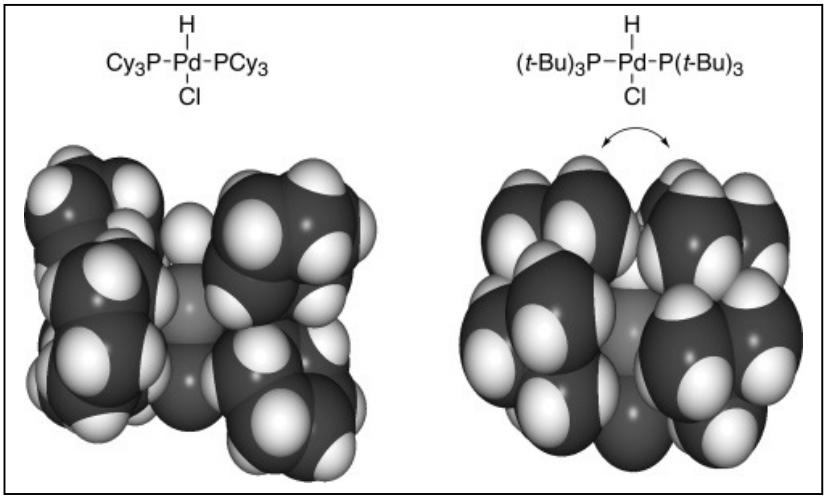


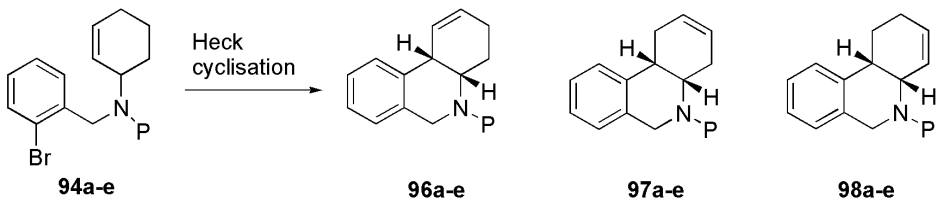

**Figure 2.5** *Space-filling models based on the X-ray crystal structures of $L_2PdHCl$ (left: L = $PCy_3$; right: L = $P(^tBu)_3$).*[95]

### 2.8.2.2 Application to protected amine cyclisation precursors

With this in mind, we explored the use of this catalyst with cyclisation precursors **94a-e** (**Table 2.8**). The intermolecular reactions are typically conducted in dioxane,[61] but the use of this solvent in our system led to very low conversions. However, a simple solvent switch to MeCN gave much more promising results albeit to a roughly equal mixture of all three double bond isomers, not to predominantly the $\Delta^{1,2}$ isomer as predicted from the mechanistic precedent.

We observed complete conversion of sulfonamide **94a** to products **96a-98a** at room temperature, however, the Boc and Cbz protected precursors **94b** and **94c** required a slightly elevated temperature (50 °C) for the cyclisation reaction to proceed to completion. Intriguingly, the Bn and PMB-protected substrates **94d** and **94e** showed little or no reactivity at either temperature.

**Table 2.8** *Cyclisation under low-temperature conditions.*[a]

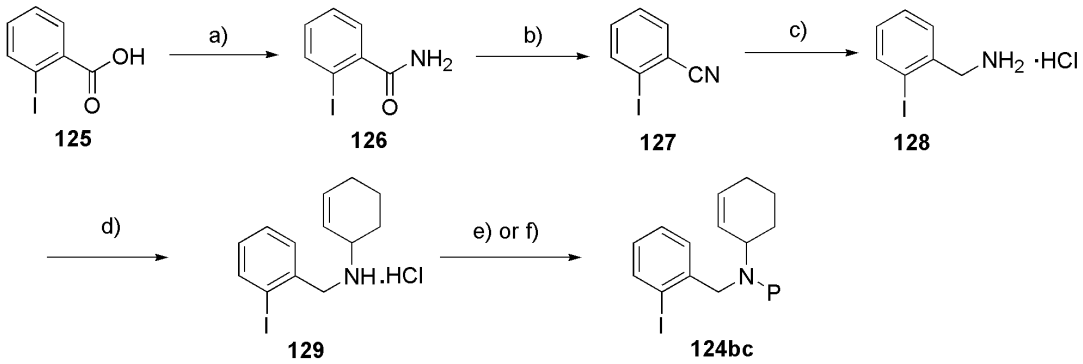



| Entry | Substrate | P | Method | t (h) | Yield (%) | Ratio (**96**:**97**:**98**) |
|---|---|---|---|---|---|---|
| **1** | **94a** | $SO_2Me$ | A | 9 | 99 | 12:65:23 |
| **2** | **94a** | $SO_2Me$ | B | 4 | 99 | 55:41:4 |
| **3** | **94b** | Boc | A | 40 | 50 | 34:43:22 |
| **4** | **94b** | Boc | B | 7 | 95 | 34:37:29 |
| **5** | **94c** | Cbz | A | 40 | 64 | 53:34:13 |
| **6** | **94c** | Cbz | B | 7 | 85 | 36:5:59 |
| **7** | **94d** | Bn | A | 72 | no reaction | -- |
| **8** | **94d** | Bn | B | 40 | 23 | n.d.[b] |
| **9** | **94e** | PMB | A | 72 | no reaction | -- |
| **10** | **94e** | PMB | B | 40 | no reaction | -- |

[a] Conditions: Method A: Aryl halide (1 eq), $Pd_2(dba)_3$ (5 mol%), $^tBu_3PHBF_4$ (10 mol%), $MeNCy_2$ (4 eq), MeCN, r.t.; Method B: As Method A at 50 °C. [b] not determined

### 2.8.2.3 Application to aryl iodides

Aryl iodides are known to undergo oxidative addition more rapidly than their bromo or chloro counterparts, so we decided to synthesise the Boc and Cbz aryl iodides to determine whether cyclisation could be facilitated at room temperature. As 2-iodobenzylamine is not commercially available, our synthesis of cyclisation precursors **124b** and **124c** started from 2-iodobenzoic acid **125** (**Scheme 2.18**). This was readily converted into the acid chloride, followed by treatment with aqueous ammonia to generate amide **126**. Dehydration of amide **126** gave nitrile **127**, which was converted into amine **128** by a $LiAlH_4$ mediated reduction. Conversion to the cyclisation precursors **124b** and **124c** proceeded in a similar manner to that previously shown.



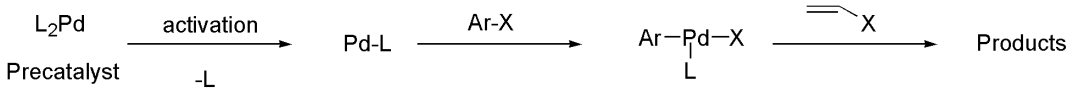

**Scheme 2.18** *Synthesis of Boc and Cbz aryl iodide cyclisation precursors.*

a i) $SOCl_2$, 60 °C, 3 h; a ii) $NH_4OH$, r.t., 16 h, 61%; b) $SOCl_2$, 60 °C, 3 h, 99%; c) $LiAlH_4$, $AlCl_3$, $Et_2O$, 40 °C, 3 h, 52%; di) $^iPr_2NEt$, 3-bromocyclohexene, MeCN, 16 h; ii) HCl in $Et_2O$, 99%; e) **124b** P=Boc, $Boc_2O$, $Et_3N$, $CH_2Cl_2$, 16 h, 49%; f) **124c** P=Cbz, NaH, DMF, 0 °C, 30 min, then benzylchloroformate, r.t., 16 h, 82%.

Surprisingly however, when we subjected aryl iodides **124b** and **124c** to the room temperature cyclisation conditions shown in **Table 2.8**, we only observed <20% conversion in each case after 16 h reaction. We were very surprised by these results and can only conclude that the additional steric bulk of the iodine on the Pd hindered the cyclisation from going to completion. Further evidence to support the incompatibility of $(^tBu_3P)_2Pd$ with bulky substrates comes from the failed cyclisation of our 3,3-dimethyl cyclisation precursor **115** at either r.t. or 50 °C using this catalyst.

### 2.8.2.4 Rationalising catalyst behaviour

While we were pleased to have an alternative set of mild conditions for our Heck cyclisation, we were puzzled as to the large degree of double bond isomerism observed, especially in light of the report illustrating the facile reductive elimination of HCl from $(^tBu_3P)_2PdHCl$.[95] Further examination of the literature suggested that when bulky phosphine ligands are employed, sterically-driven dissociation of one ligand occurs prior to the oxidative addition, giving rise to a mono-ligated Pd(0) (**Scheme 2.19**).[60] If such a mono-ligated Pd(0) is the catalytically active species, then clearly the above arguments regarding steric-promoted reductive elimination are not valid, perhaps rationalising why double bond isomerism was not minimised.




**Scheme 2.19** *Generation and reaction of a mono-ligated Pd(0).*[60]

L = Bulky phosphane with high σ-donicity; X= I, Br, Cl, OTs, OTf.

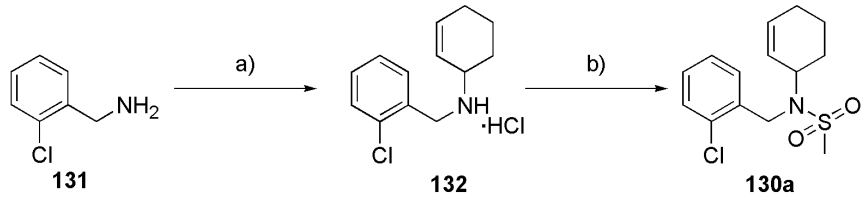
It is clear both from our results and from the literature precedent, that this mono-ligated Pd(0) species is also a highly reactive catalyst. It has long been proposed that high reactivity (TON) in the Heck reaction arises from coordinative unsaturation at Pd(II).[96] Indeed, pre-dissociation of 16e-Pd(II) complexes to yield coordinatively unsaturated 14e-Pd(II) intermediates have been convincingly shown to offer a low free-energy pathway to transmetallation.[97] It seems plausible therefore to suggest that weak σ-donor ligands as opposed to strong σ-donor ligands (such as the trialkylphosphines), would lead to more rapid ligand dissociation and coordinative unsaturation. However, contrary to this, trialkylphosphine ligands *are* able to rapidly generate mono-ligated Pd(0) species, but this arises not from their σ-donor capability but rather from their ability to create coordinative unsaturation by steric bulk. This creates a very powerful catalytic species that is further stabilised by the strong σ-donicity of the ligand.

The coordinatively unsaturated nature of the L-Pd(0) species renders it highly reactive toward oxidative addition. This permits the successful Pd-mediated cross-coupling of typically unreactive substrates e.g aryl chlorides, and electron-rich aromatics, and also permits the Heck reaction to be performed at non-elevated temperatures as we have observed.

Although we had initially employed the $(^tBu_3P)_2Pd$ catalyst system in an attempt to obtain one isomer product, we realised the potential our results offered toward our DOS library as complementary set of conditions for the cyclisation of thermally unstable and poorly reactive substrates.

### 2.8.3 Attempted cyclisation of an aryl chloride precursor

In light of the literature reports illustrating the low temperature (<50 °C) intermolecular Heck coupling of aryl chlorides using $(^tBu_3P)_2Pd$,[61,62] we were curious to examine what effect the catalyst system would have on an aryl chloride variant of our cyclisation precursor. Aryl chloride **130a** was synthesised in a similar manner to its bromo and iodo counterparts, via alkylation of commercially available 2-chlorobenzylamine with 3-bromocyclohexene, followed by methylsulfonylation of the secondary amine **132**.



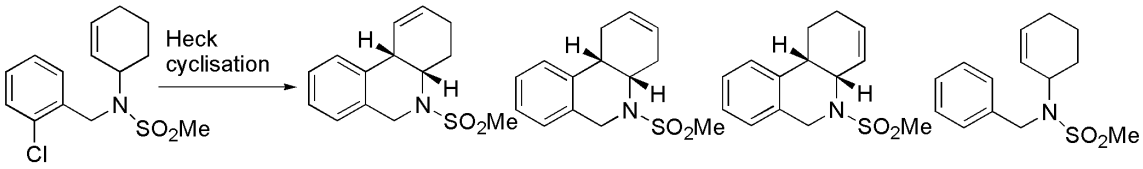

**Scheme 2.20** *Synthesis of an aryl chloride cyclisation precursor **130a**.*

a i) $^iPr_2NEt$, 3-bromocyclohexene, MeCN, 16 h; a ii) HCl in $Et_2O$, 66%. b) $MeSO_2Cl$, $Et_3N$, $CH_2Cl_2$, r.t., 16 h, 60%.

We first examined the cyclisation of aryl chloride **130a** using dioxane as the solvent, but we observed no reaction (**Table 2.9**) at either r.t. or 120 °C. Switching the solvent for MeCN did little to improve the situation, giving only trace conversions (<1%) at both r.t. and 50 °C. We decided to employ our Herrmann-Beller palladacycle conditions since we had no success with the $(^tBu_3P)_2Pd$ catalyst. Under cationic conditions we observed only 8% conversion after 16 h, and using the neutral system

we observed 15% conversion, although 11% of this was composed of the dehalogenated product **99a**.

**Table 2.9** *Study of Heck cyclisation conditions for aryl chloride **130a**.*




**130a** **96a** **97a** **98a** **99a**

| Entry | Conditions[a] | T (°C) | t (h) | Solvent | Conversion (%)[b] | Ratio **96a:97a:98a:99a** |
|---|---|---|---|---|---|---|
| **1** | $Pd_2(dba)_3$, $^tBu_3PHBF_4$, $MeNCy_2$ | r.t | 16 | dioxane | 0 | - |
| **2** | $Pd_2(dba)_3$, $^tBu_3PHBF_4$, $MeNCy_2$ | 120 | 16 | dioxane | 0 | - |
| **3** | $Pd_2(dba)_3$, $^tBu_3PHBF_4$, $MeNCy_2$ | r.t | 16 | MeCN | Trace | - |
| **4** | $Pd_2(dba)_3$, $^tBu_3PHBF_4$, $MeNCy_2$ | 50 | 16 | MeCN | Trace | - |
| **5** | Palladacycle **100**, $Ag_2CO_3$ | 140 | 16 | DMF | 8 | n.d |
| **6** | Palladacycle **100**, $MeNCy_2$ | 140 | 16 | DMF | 15 | 27:0:0:73 |
| **7** | Palladacycle **100**, $MeNCy_2$ $^t$BuNBr | 140 | 16 | DMF | - | - |
| **8** | $Pd_2(dba)_3$, $^tBu_3PHBF_4$, NaOAc | 150 | 16 | $^t$BuNBr | - | - |

[a] [5 mol% Pd(0) source] / [10 mol% ligand] [b] Conversion was determined through analysis of the $^1$H NMR of the crude reaction mixture.

We examined the literature and discovered no reports of $(^tBu_3P)_2Pd$ being successfully employed in the intramolecular Heck reaction of an aryl chloride and only three examples of different catalyst systems being used for such a purpose.[98-100] Two of these literature reports employed the use of one equivalent of tetra-*n*-butylammonium bromide or chloride to achieve poor to moderate conversions (28-70%), but when we tried this on our palladacycle catalysed neutral conditions we observed no trace of cyclisation (entry **7**).[98] The other report also used tetra-*n*-butylammonium bromide, but this time as the solvent.[99]. However, again we observed no conversion using this method (entry **8**).

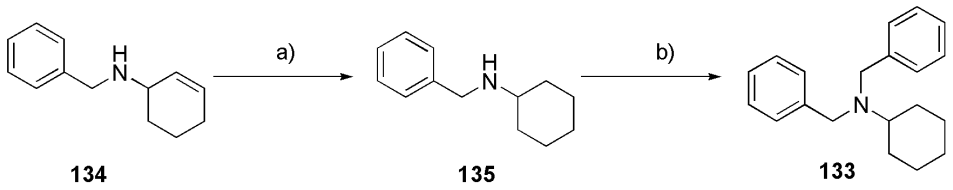
Therefore we were unable in our short investigation to generate reaction conditions for the cyclisation of aryl chloride **130a**. The abundance of aryl chloride building blocks commercially available (as opposed to iodides and bromides) would make this area very worthwhile for further investigation, especially in light of the lack of successful conditions in the literature.

## 2.9 Mechanistic studies

### 2.9.1 Amine cyclisation precursors

The first mechanistic issue we wished to address was the minimal double bond isomerism observed upon the cyclisation of amine substrates **94d** and **94e** as opposed to sulfonamide and carbamate substrates **94a-c**. Under cationic conditions both the amine cyclisations showed exceptional selectivity for the $\Delta^{1,2}$ isomer, well in excess of the amide substrates. Under the palladacycle catalysed neutral conditions, **94d** and **94e** both gave strong selectivity for the $\Delta^{1,2}$ isomer whereas the amide substrates gave a spread of the different isomer products. Additionally, they also showed minimal reactivity under the $(^tBu_3P)_2Pd$ catalysed conditions, as compared to the amide substrates.

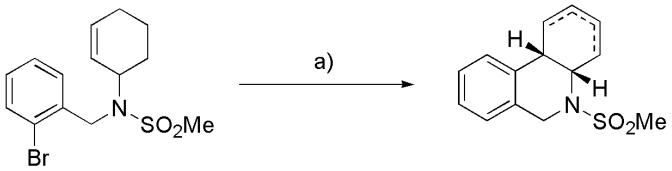
We postulated that perhaps in the cyclisation of these amine precursors, the substrates themselves were acting as bases, capable of minimising isomerism. In order to test this theory we decided to synthesise dibenzylcyclohexylamine[100] **133**, a simplified analogue of the benzyl protected cyclisation precursor **94d** and use this instead of $MeNCy_2$ as the base in one of our amide Heck cyclisations.




**Scheme 2.21** *Synthesis of dibenzylcyclohexylamine **133**.*[100]

a i) Benzyl bromide, NaH, 16 h, r.t; a ii) $H_2$, Pd/C, MeOH/EtOAc, 16 h, r.t., 63%; b) BnBr, NaH, 16 h, r.t., 82%.

We chose to test it on the cyclisation of sulfonamide analogue **94a** as this gave rise to diverse range of double bond isomers under our standard neutral conditions and would provide a suitable comparison (**Scheme 2.22**). However, we discovered that while dibenzylcyclohexylamine[100] proved to be an excellent base with regard to conversion (100%), it furnished significant quantities of each of double bond isomers **96a**-**98a**.




**94a** **96a-98a 42:29:29**

**Scheme 2.22** *Testing dibenzylcyclohexylamine*[100] *as a base for the Heck reaction.*

a) Palladacycle **100** (5 mol%), $Bn_2NCy$ **133** (4 eq), DMF, 140 °C, 16 h, 99%.

The investigation shown in **Scheme 2.22** dismisses the possibility of substrates **94d** and **94e** acting as bases intermolecularly, but not intramolecularly. Following β-hydride elimination, the Pd-H species ends up on the same face of the cyclohexene ring system as the amine nitrogen functionality. The close proximity of the amine nitrogen to the Pd-H species means that intramolecular reductive elimination could be facilitated rapidly, resulting in minimal double bond isomerism. This hypothesis could be examined by studying the cyclisation of substrates **94d** or **94e** in the absence of base.

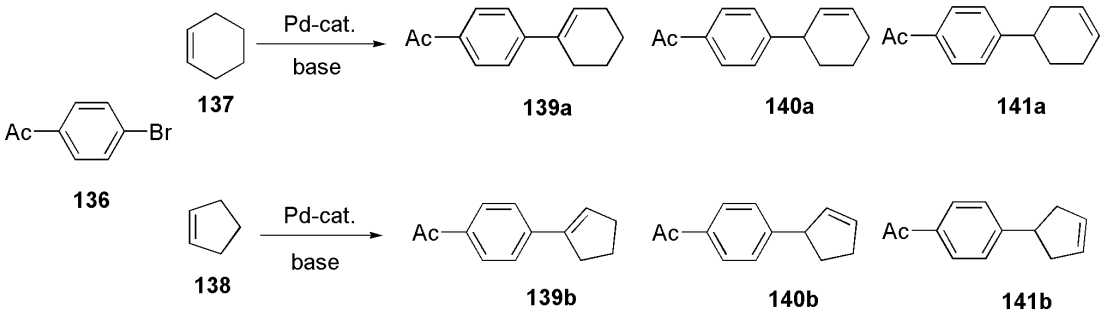
### 2.9.2 Sulfonamide and carbamate substrates

We have shown very different results with regard to the double bond isomer ratio obtained for the sulfonamide and carbamate precursor cyclisations, using each of our optimised reaction conditions. In the case of the cationic cyclisation this can be easily rationalised as arising from the rapid reductive elimination step, as reported in **section 2.4**. However, under the neutral conditions, the double bond isomer profile obtained using different catalysts ($Pd(OAc)_2$, palladacycle **100**, and ($^tBu_3P)_2Pd$) shows dramatic variation, (*e.g.* from 92:6:2 to 33:39:28 for cyclisation of **94a**), that cannot be so easily rationalised.

Beller has concluded that in the intermolecular Heck reaction of arylbromides with cyclohexene and cyclopentene, double bond migration is predominantly catalysed by the base used in the reaction, and not by a HPdX complex (**Table 2.10**).[101] In this simple intermolecular study, the choice of solvent (entry **1** vs **3**) and base (entries **1** vs **2** and **5** vs **6**) was shown to have an important influence on the extent of C-C double bond migration, whilst different catalysts showed no significant changes in

selectivity (entries **1** vs **4** and **6** vs **7**). It may be argued that the electron-withdrawing nature of the acetate group aids base-catalysed isomerism, however similar variation in the double bond isomer ratio was also observed for other aryl bromides (*m*-$CF_3$, *p*-OMe, phenyl).

**Table 2.10** *Base/Solvent catalysed double bond isomerism of cycloalkenes.*[101]




| Entry | Cycloalkene | Solvent | Catalyst[a] | Base[b] | Conversion (%) | Ratio **139:140:141** |
|---|---|---|---|---|---|---|
| 1 | **137** | DMA | $Pd(OAc)_2/2PPh_3$ | NaOAc | 96 | 4:17:79 |
| 2 | **137** | DMA | $Pd(OAc)_2/2PPh_3$ | $^iPr_2NEt$ | 63 | 1:33:66 |
| 3 | **137** | DMSO:DMA (4:1) | $Pd(OAc)_2/2PPh_3$ | NaOAc | 59 | 2:8:90 |
| 4 | **137** | DMA | Palladacycle **100** | NaOAc | 89 | 7:15:78 |
| 5 | **138** | DMA | $Pd_2(dba)_3.dba/PCy_3$ | NaOAc | 99 | 39:45:16 |
| 6 | **138** | DMA | $Pd_2(dba)_3.dba/PCy_3$ | $Na_2CO_3$ | 99 | 91:7:2 |
| 7 | **138** | DMA | $Pd(OAc)_2/2PPh_3$ | $Na_2CO_3$ | 98 | 83:13:4 |

[a] [5 mol% Pd(0) source]; [b] 1 eq base, 120-140 °C.

In sharp contrast, our study demonstrates that in the intramolecular neutral Heck reaction where the two components are linked as the protected benzylamine, the palladium catalyst plays a pivotal role in double bond isomerism under otherwise identical conditions ($Pd(OAc)_2$ vs HB or $(^tBu_3P)_2Pd$, with $MeNCy_2$ in DMF). To further probe why different catalysts were giving rise to such different results, we carried out a series of mechanistic studies.

### 2.9.3 Isomer variation with time

To determine at what point isomerism occurred, we monitored the double bond isomer ratio with time for each of our optimised reactions using sulfonamide cyclisation precursor **94a**. Aliquots were taken from each reaction at the appropriate timepoint and the composition was analysed using $^{1}$H NMR spectroscopy. Integration of the three double bond isomer peaks highlighted in **section 2.5**, allowed us to plot the following graphs.

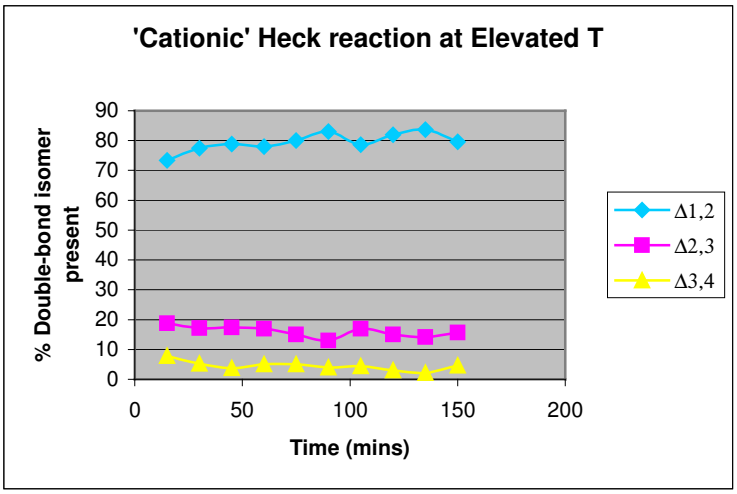



**Figure 2.6** *Isomer variation for cationic cyclisation of* ***94a*** *using palladacycle* ***100***.
Conditions: **94a** (1 eq), palladacycle **100** (5 mol%), $Ag_2CO_3$ (1 eq), DMF, 140 °C

First of all we monitored the cationic cyclisation using the Herrmann-Beller palladacycle (**Figure 2.6**). The graph clearly shows that the $\Delta^{1,2}$ isomer is the major product at all times, holding true to the theory of rapid reductive elimination. With this reaction, no change in double bond isomer ratio is visible after the onset of the reaction, suggesting that once decomplexation of the catalyst occurs from the alkene, no recomplexation and subsequent isomerism occurs.

We next examined the Hermann-Beller palladacycle under neutral conditions (**Figure 2.7**). This graph illustrates an initial induction period (0-90 mins) where some variation in the $\Delta^{1,2}$ to $\Delta^{2,3}$ ratio occurs. After this point however, no significant variation in the ratio of the products is observed even though the reaction takes up to

180 minutes to reach completion (**Table 2.3**, entry **2**). This again suggests that once the catalyst has decomplexed from the alkene, no further isomerism occurs.

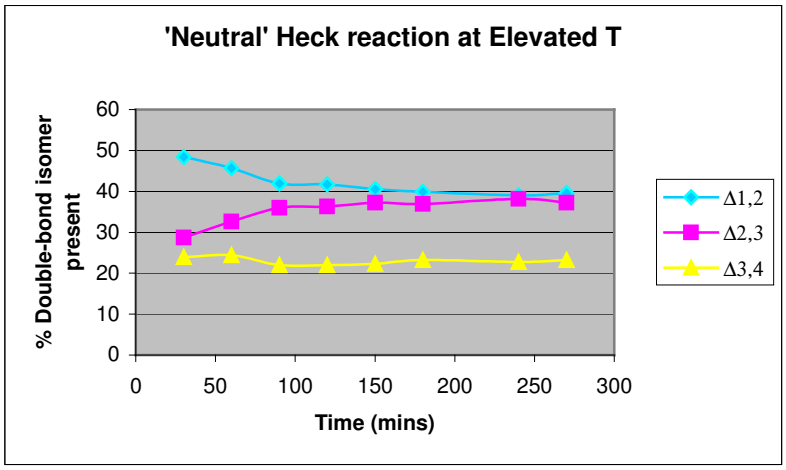



**Figure 2.7** *Isomer variation for neutral cyclisation of* ***94a*** *using palladacycle* ***100****.*
Conditions: ArBr (1 eq), $MeNCy_2$ (4 eq), palladacycle **100** (5 mol%), DMF, 140 °C.

Finally, we studied the $(^tBu_3P)_2Pd$ catalysed cyclisation (**Figure 2.8**) at room temperature, which clearly shows that the $\Delta^{2,3}$ isomer is the favoured product from the outset of the reaction and that there is essentially no change in double bond isomer ratio from the outset of the reaction.

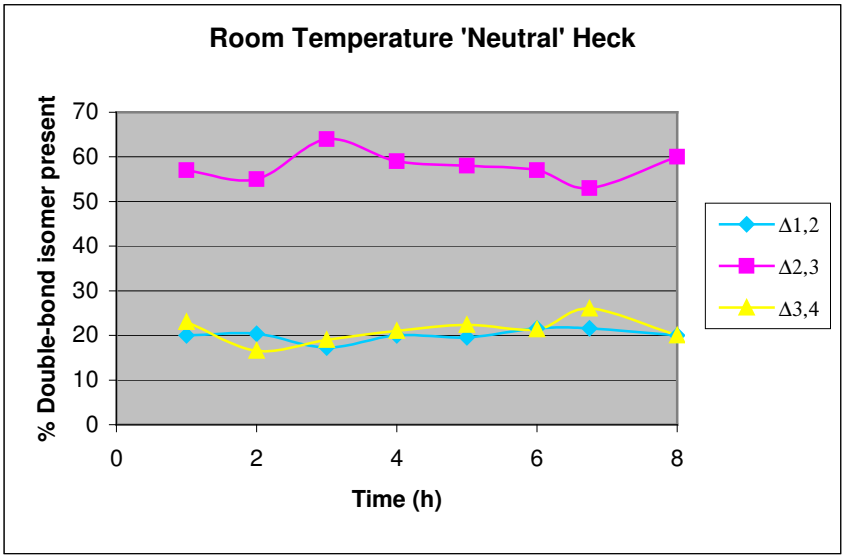
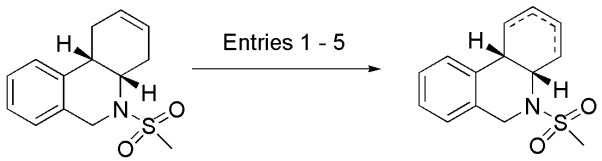



**Figure 2.8** *Isomer variation for neutral cyclisation of* ***94a*** *using* $(^tBu_3P)_2Pd$*.*
Conditions: ArBr (1 eq), $Pd_2(dba)_3$ (5 mol%), $^tBu_3PHBF_4$ (10 mol %), $MeNCy_2$ (4 eq), MeCN, r.t.

### 2.9.4 Resubmission experiments

The double bond isomer ratio monitoring experiments all suggest that further isomerism does not occur once the catalyst has decomplexed from the alkene. To test this hypothesis we decided to execute a series of experiments where the sulfonamide $\Delta^{2,3}$ isomer **97a** was resubmitted to the optimised reaction conditions to observe if isomerism had occurred (**Table 2.11**). In addition to probing our decomplexation hypothesis, these studies also gave us the opportunity to observe whether double bond isomerism was base-catalysed.[101]

**Table 2.11** *Resubmission experiments*.




| Entry | Conditions | T (°C) | T (h) | Ratio (96a:97a:98a) |
|---|---|---|---|---|
| **1** | Palladacycle **100**, $MeNCy_2$, DMF | 140 | 16 | 0: 100: 0 |
| **2** | Palladacycle **100**, $Ag_2CO_3$, DMF | 140 | 16 | 0: 100: 0 |
| **3** | $Pd_2(dba)_3$, $^tBu_3PHBF_4$, $MeNCy_2$ MeCN | r.t | 72 | 0: 100: 0 |
| **4** | Palladacycle **100**, $MeNCy_2$, DMF, HBr (1 eq) | 140 | 72 | 4: 96: 0 |
| **5** | $CH_3COOH$ (excess), DMF | 140 | 72 | 19: 78: 8 |

[a] [5 mol% Pd(0) source] [b] Conversion was determined through analysis of the $^1H$ NMR of the crude reaction mixture.

Resubmission of sulfonamide $\Delta^{2,3}$ isomer **97a** to each of the three optimised conditions (entries **1**-**3**) resulted in no double bond isomerism. Each of these conditions should have permitted double bond migration to occur if, it were base-catalysed, so clearly in our case double bond isomerism results from other factors.

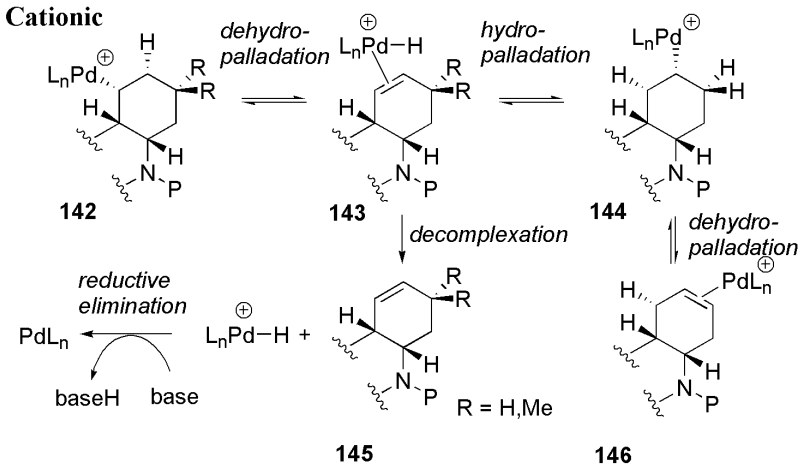
Although entries **1**-**3** suggest that no isomerism occurs following decomplexation, we had concerns that we had not taken into account the equivalent of HBr liberated during the reductive elimination process. We wondered if the catalyst system was able to turn over without this present, and whether our simple resubmission experiment was an accurate reflection of the environment faced by an alkene

following reductive elimination. We repeated the resubmission of sulfonamide $\Delta^{2,3}$ isomer **97a** to the neutral palladacycle catalysed conditions, this time including one equivalent of HBr. As indicated in **Table 2.11** slight double bond isomerism was observed, but the extent of this did not explain the ratios observed under normal cyclisation circumstances, especially since the time period of the current experiment was significantly longer (72 h vs 6 h).

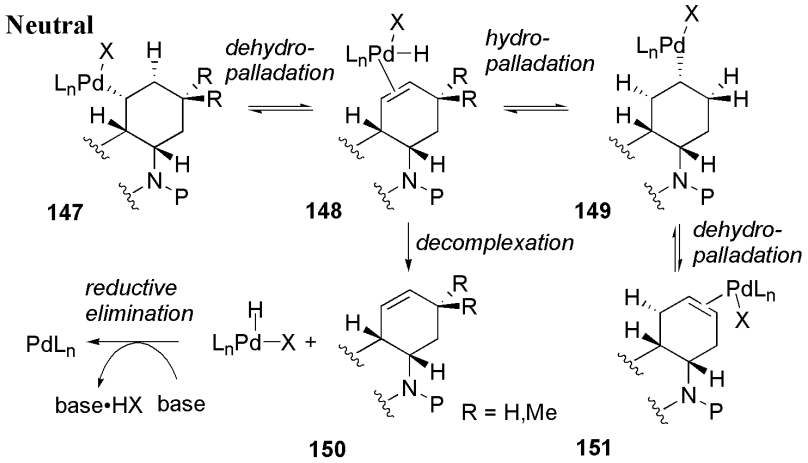
Out of interest, we examined the effect of acid on our phenanthridine system (entry **5**) and the results clearly show that a significant proportion of the sulfonamide $\Delta^{2,3}$ isomer **97a** undergoes conversion to the other isomers after 72 hours at elevated temperature. Although this has no bearing on our cyclisation reactions, it is an interesting result, which is in contrast to the previous report that isomerism in an intermolecular reactions is base-catalysed.[101] In light of this result we propose that the minimal isomerism observed in the HBr resubmission experiment (entry **4**) is actually a result of acid-catalysed migration.

### 2.9.5 Decomplexation vs hydro/dehydropalladation

From these results, it must therefore be concluded that the double bond isomer ratio is established at the outset of the reaction, and does not change following decomplexation of the catalyst from the alkene. The double bond isomer ratio obtained in these intramolecular Heck cyclisation reactions must therefore be a product of the differing rates of decomplexation of each catalyst as compared to the rate of hydro-palladation/dehydropalladation (**Scheme 2.23** and **Scheme 2.24**).[102]




**Scheme 2.23** *Hydro-palladation/dehydro-palladation for the cationic reaction.*




**Scheme 2.24** *Hydro-palladation/dehydro-palladation for the neutral reaction.*

## 2.10 Conclusions

We have successfully investigated and developed conditions for the Heck cyclisation of various sulfonamide, carbamate and amine precursors to give phenanthridines.[49] If one double bond isomer is required, the reaction can be performed under cationic conditions using the Herrmann-Beller palladacycle **100** to give predominantly the $\Delta^{1,2}$ isomer. These conditions have been shown to achieve high yielding conversions (76-99%) to the Heck products in less than two hours, and have proved successful in a system with additional steric bulk on the cyclohexenyl ring.

We have also developed two sets of conditions for the synthesis of a mixture of phenanthridine double bond isomers using the Heck reaction, which we intend to utilise in the preparation of a DOS library (**Chapters 3** and **4**). Palladacycle **100** can be employed at elevated temperature using the sulfonamide and carbamate substrates to give the desired product mixture in less than 5 hours, with excellent yield (93-99%). Alternatively, the highly reactive Fu catalyst $(^{t}Bu_3P)_2Pd$ can be used for the low temperature (r.t. or 50 $^{o}C$) cyclisation of the sulfonamide and carbamate precursors, to give the double bond isomer mixture in less than 9 hours and with excellent conversions (85-99%).

We found that careful choice of the catalyst and reaction conditions employed had a significant effect on the outcome of the products, and our mechanistic investigations attribute this to either a cationic vs neutral pathway, or differing rates of decomplexation as compared to the rate of hydro-palladation/dehydropalladation for each catalyst, depending on the particular reaction in question.

# *RESULTS AND DISCUSSION PART 2*
# CHAPTER 3

## DIVERSIFICATION METHODOLOGY

### 3.1 Introduction

As discussed in **Chapter 2**, we realised the potential our two sets of neutral cyclisation conditions had toward the development of a DOS library. Each cyclisation performed under these conditions furnished three skeletons, each with an alkene handle suitable for further functionalisation.[49] In addition to this, further incorporation of diversity could be accomplished by any of the three means outlined in **Chapter 1**, namely appendage (or building block) variation, introduction of stereochemistry, or by further skeletal diversification.

Building block variation of the A-ring was investigated through the synthesis (and subsequent cyclisation) of various aryl and heteroaryl Heck cyclisation precursors. We chose to investigate the introduction of stereochemical diversity by examining dihydroxylation protocols for the C-ring phenanthridine double-bond isomers. Finally, the introduction of skeletal diversity was examined using novel ring-rearrangement metathesis reactions of the phenanthridine C-ring (**Figure 3.1**).

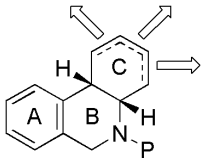



**Figure 3.1** *Introducing diversity to the phenanthridine core.*

P= Protecting group.

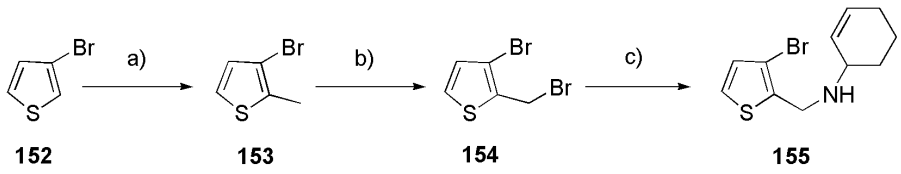
### 3.2 Building Block Diversity

We realised that the aromatic part of our phenanthridine core ring structure was an excellent component through which to investigate building block diversity. To this end we set about synthesising a range of suitable aromatic and heteroaromatic cyclisation precursors.

#### 3.2.1 Thiophene analogue

Initial investigations in the area of building block diversity were based around the synthesis of a heteroaromatic thiophene equivalent of our standard sulfonamide protected phenanthridines **96a-98a**. As a result we developed two synthetic routes to incorporate the heteroaromatic building block, both of which warrant discussion despite not being used in our final DOS library synthesis.

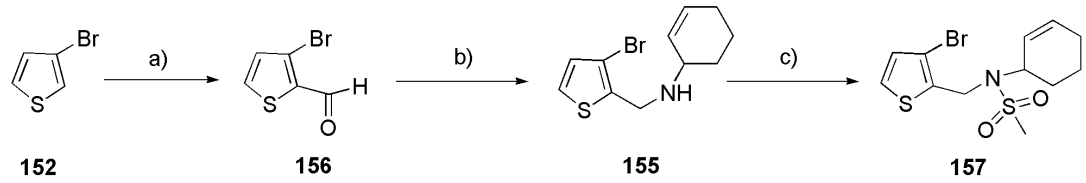
Our first synthetic strategy started with methylation of 3-bromothiophene **152** to afford 2-methylthiophene **153** in excellent yield.[103] This was followed by a radical bromination using NBS/AIBN to afford thiophenemethyl bromide **154**.[104] Attempted monoalkylation of 3-aminocyclohexene[105] with thiophenemethyl bromide **154** proceeded poorly giving the desired secondary amine in only 18% yield (**Scheme 3.1**). This poor yield, coupled with the undesirable use of $CCl_4$ earlier in the synthetic route, led us to investigate an alternative synthesis of amine **155**.




**Scheme 3.1** *First generation synthesis of a thiophene analogue.*

a) i) LDA, THF, 0 $^{o}$C → -78 $^{o}$C, 0.5 h; ii) MeI, -70 $^{o}$C, 0.5 h, then r.t., 1 h, 99%; b) AIBN, NBS, $CCl_4$, 80 $^{o}$C, 3 h, 53%; c) 3-aminocyclohexene, $^{i}Pr_2NEt$, MeCN, r.t., 16 h, 18%.

Our second generation synthesis also began using 3-bromothiophene **152**, this time performing an α-lithiation followed by anion trapping with DMF to afford carbaldehyde **156** in excellent yield (**Scheme 3.2**).[106] The initial lithiation step must be performed at 0 °C as the competitive formation of the 5-lithiated thiophene is known to occur at -78 °C. We next attempted a reductive amination using 3-aminocyclohexene[105] but as in the first generation synthesis, secondary amine **155** was obtained in very poor yield.[107] The 3-aminocyclohexene used in both the coupling protocols was difficult to synthesise and purify, and we propose that this resulted in the poor conversions we observed in both cases.

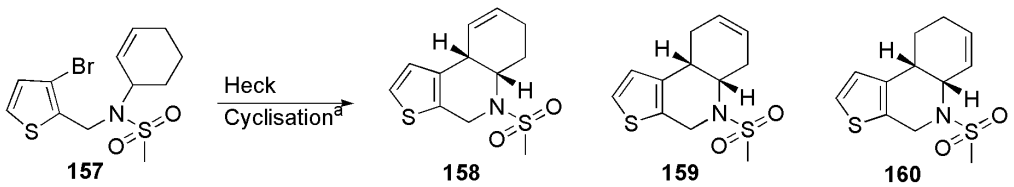



**Scheme 3.2** *Second generation synthesis of a thiophene analogue.*

a) i) LDA, THF, 0 °C, 0.5 h; ii) DMF, 0 °C → r.t., 2.5 h, 94%; b) i) 3-aminocyclohexene, $^{i}Pr_2NEt$, PhMe, mol. sieves, 110 °C, 16 h; ii) $Na(OAc)_3BH$, MeOH, 16 h, r.t., 16%; c) $MeSO_2Cl$, $Et_3N$, $CH_2Cl_2$, r.t., 16 h, 68%.

Although neither route had proved to be particularly successful, we did manage to obtain sufficient quantities of amine **155** to take on in the synthetic sequence, and so sulfonamide **157** was synthesised in good yield using the previously reported conditions, giving us material to test our Heck cyclisation upon (**Table 3.1**).

**Table 3.1** *Heck cyclisation of thiophene analogues **158-160**.*




| Entry | Conditions[a] | T (°C) | t (h) | Solvent | Conversion (%)[b] | Ratio **158:159:160** |
|---|---|---|---|---|---|---|
| 1 | Palladacycle **100**, $Ag_2CO_3$ | 140 | 2 | DMF | 91 | 77:16:7 |
| 2 | Palladacycle **100**, $MeNCy_2$ | 140 | 4 | DMF | 74 | 32:41:27 |
| 3 | $Pd_2(dba)_3$, $^{t}Bu_3PHBF_4$, $MeNCy_2$ | r.t | 18 | MeCN | 25 | 80:20:n.d.[c] |
| 4 | $Pd_2(dba)_3$, $^{t}Bu_3PHBF_4$, $MeNCy_2$ | 50 | 16 | MeCN | 55 | 76:15:9 |

[a] 5 mol% Pd(0) source, 10 mol% ligand. [b] Conversion was determined through analysis of the $^1$H NMR of the crude reaction mixture. [c] n.d. not determined.

We were pleased to discover that both of our palladacycle-catalysed Heck cyclisation conditions proved to be robust for this heteroaromatic analogue, giving similar reactivities and double bond isomer ratios to the aromatic substrates studied previously. Interestingly, $(^tBu_3P)_2Pd$ did not prove to be particularly reactive on heteroaromatic analogue **157**, despite the success it had shown with the aromatic amides (see section **2.8.2**), and unfortunately our best result was only 55% conversion at 50 °C (entry **4**). Additionally, we were surprised to see that the double bond isomer ratio for this neutral cyclisation was in keeping with the cationic cyclisation, quite unexpected for $(^tBu_3P)_2Pd$, given the precedent in the previous chapter.

Regardless of the $(^tBu_3P)_2Pd$ results, we were confident that both our palladacycle **100** catalysed conditions would prove successful across a range of aryl/heteroaryl analogues, so our next aim was to develop higher yielding route to the synthesis of such cyclisation precursors.

### 3.2.2 Standard synthesis of aryl amines

We had previously used several standard transformations to synthesise aryl iodides **124b** and **124c** from 2-iodobenzoic acid **125** (**Scheme 2.18**), so we took another look at this approach. In order for this to be viable we needed to identify a wide range of commercially available 2-bromobenzoic acid starting materials, and fortunately there were several available (**Figure 3.2**). In addition to benzoic acids, we identified two suitable heteroaromatic starting materials **161f** and **161h**, as well as 2-bromophenylacetic acid **161j** that would potentially allow us to examine the synthesis of a 7-membered B–ring phenanthridine.

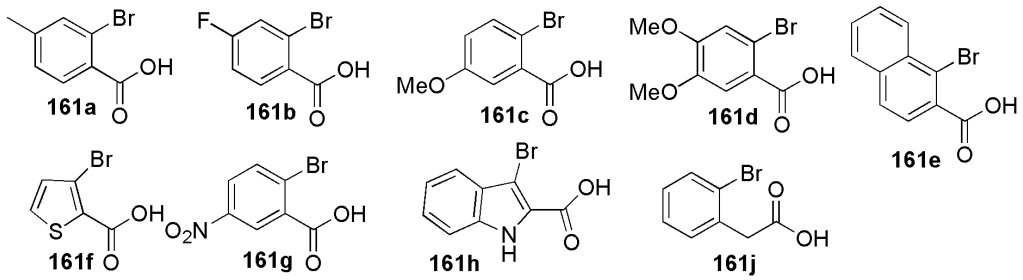
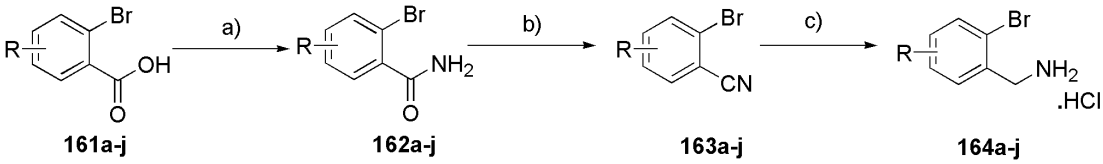



**Figure 3.2** *Some commercially available benzoic acids.*

Application of the standard transformations developed in **Chapter 2** proved compatible with the majority of the substrates (**Table 3.2**) although there were a few exceptions. Unfortunately the 5-$NO_2$ nitrile analogue **163g** was not tolerant of the harsh $LiAlH_4$ reducing conditions so we did not pursue the synthesis of this analogue any further. Both the indole substrate and the phenethyl substrate required direct treatment of the amide substrate (**162h** or **162j**) with $LiAlH_4$ to generate the desired amine. In the case of the phenethyl substrate this was poorly yielding (14%) and we performed the reaction in THF rather than $Et_2O$, to achieve a higher conversion (75%). An alternative approach to phenethyl substrate was developed later in this work (see **section 3.2.5**) and the problems associated with the synthesis of the indole analogue are addressed in **section 3.2.6**.

**Table 3.2** *Synthesis of amine building blocks.*




**161a-j** **162a-j** **163a-j** **164a-j**

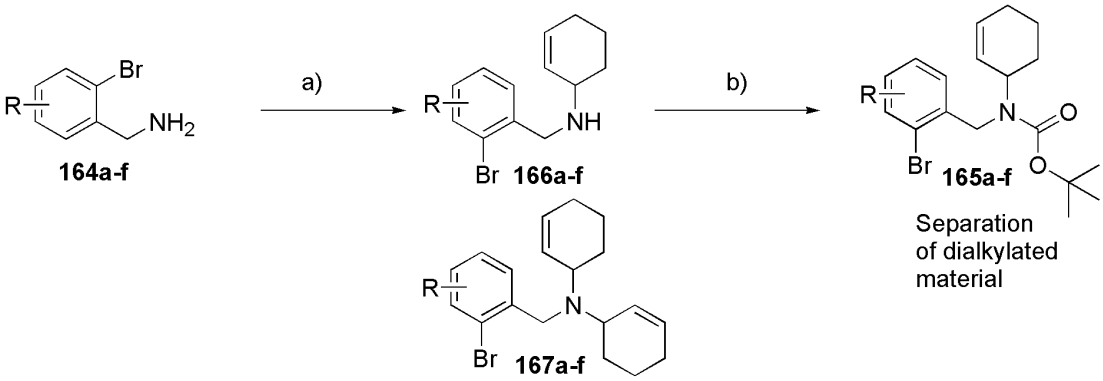
| Entry | 161 | Substrate (R= ) | Yield (% ) 162 | Yield (% ) 163 | Yield (%) 164 |
|---|---|---|---|---|---|
| 1 | **a** | 4-Me | 95 | 73 | 80 |
| 2 | **b** | 4-F | 94 | 97 | 70 |
| 3 | **c** | 5-MeO | 73 | 99 | 65 |
| 4 | **d** | 4,5-MeO | 99 | 88 | 74 |
| 5 | **e** | [*Naphthyl*]$^{\$}$ | 99 | 95 | 55 |
| 6 | **f** | [*Thiophene*]$^{\$}$ | 93 | 99 | 89 |
| 7 | **g** | 5-$NO_2$ | 99 | 99 | - |
| 8 | **h** | [*Indole*]$^{\$}$ | 98 | - | 55$^{a,b}$ |
| 9 | **j** | [*Phenethyl*]$^{\$}$ | 74 | - | 75$^{a,c}$ |

a) i) $SOCl_2$, 60 $^{o}$C, 3 h; ii) $NH_4OH$, r.t., 16 h; b) $SOCl_2$, 60 $^{o}$C, 3 h; c) i) $LiAlH_4$, $AlCl_3$, $Et_2O$, Δ, 16 h; ii) HCl in $Et_2O$. $^{a}$ By direct reduction of the amide. $^{b}$ 3.06:1 ratio amine:debrominated material (see **section 3.2.6**). $^{c}$ In THF, with no $AlCl_3$. $^{\$}$ For simplicity, the scheme depicts a benzene ring substrate core, however where the substrate core is a hetero- or bicyclo-aromatic ring (cf **Figure 3.2**) this is signified by the parenthesised, italicised core name. This table and scheme should be read in conjunction with **Figure 3.2**.

### 3.2.3 Synthesis of cyclisation precursors.

With a range of amine hydrochlorides in hand we next examined construction of the cyclisation precursors. We decided to synthesise the Boc–protected analogues **165a-f** since the parent Boc-cyclisation precursor **94b** had proved reliable under both the cationic and neutral cyclisation conditions, and we envisaged easy removal of the Boc group to give the free amine phenanthridines. In the previous chapter, synthesis of the Boc-protected analogue was pursued via the secondary amine, so we proceeded to apply this to our range of amine substrates. Intriguingly, we observed approximately a 75:25 ratio of the mono-alkylated **166a-f** to dialkylated product **167a-f** (**Table 3.3**), something we had detected no trace of in the simple benzyl system. Alternative protocols for the selective mono-alkylation of primary amines have been reported, including CsOH promoted conditions,[108] however such procedures were not pursued due to the success of an alternative strategy discussed below.

**Table 3.3** *Dialkylation of amines **164a-f**.*

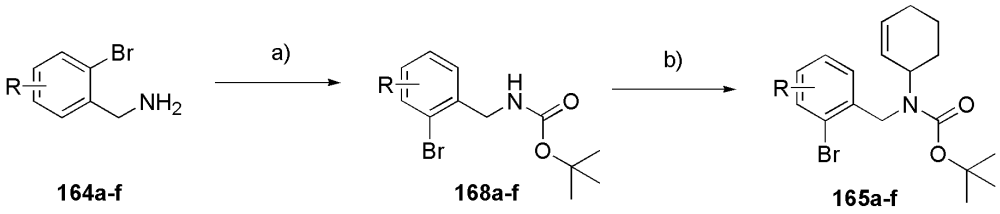



| Entry | 164 | Substrate (R= ) | Ratio 166:167 | Yield (% ) Over 2 steps 165 |
|---|---|---|---|---|
| 1 | **a** | 4-Me | 84:16 | 59 |
| 2 | **b** | 4-F | 75:25 | 68 |
| 3 | **c** | 5-MeO | 75:25 | 58 |
| 4 | **d** | 4,5-MeO | 75:25 | 56 |
| 5 | **e** | [*Naphthyl*]$^{\$}$ | 70:30 | 61 |
| 6 | **f** | [*Thiophene*]$^{\$}$ | 80:20 | 65 |

a) $^{i}Pr_2NEt$, 3-bromocyclohexene, MeCN, r.t., 16 h; b) $Boc_2O$, $Et_3N$, $CH_2Cl_2$, 16 h. $^{\$}$ See footnote to **Table 3.2**.

Although dialkylated material **167a-f** could be separated from the Boc-protected material **165a-f**, we realised that a Boc-protection then alkylation protocol, would allow us to circumvent the dialkylation problem. We found this to be a successful protocol across all our substrates **164a-f** (**Table 3.4**) giving us higher conversions over the two steps in the majority of cases.

**Table 3.4** *An alternative preparation of cyclisation precursors **165a-f.***




**164a-f** **168a-f** **165a-f**

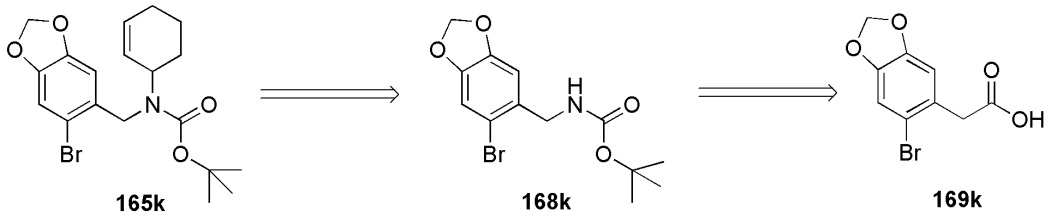
| Entry | 164 | Substrate (R= ) | Yield 168 (%) | Yield 165 (%) |
|---|---|---|---|---|
| 1 | **a** | 4-Me | 99 | 70 |
| 2 | **b** | 4-F | 88 | 71 |
| 3 | **c** | 5-MeO | 85 | 72 |
| 4 | **d** | 4,5-MeO | 99 | 84 |
| 5 | **e** | [*Naphthyl*]$^{\$}$ | 90 | 86 |
| 6 | **f** | [*Thiophene*]$^{\$}$ | 70 | 91 |

a) $Boc_2O$, $Et_3N$, $CH_2Cl_2$, 16 h; b) NaH, 3-bromocyclohexene, DMF, 0 $^{o}$C- r.t., 16 h. $^{\$}$ See footnote to **Table 3.2**.

### 3.2.4 Piperonyl analogue

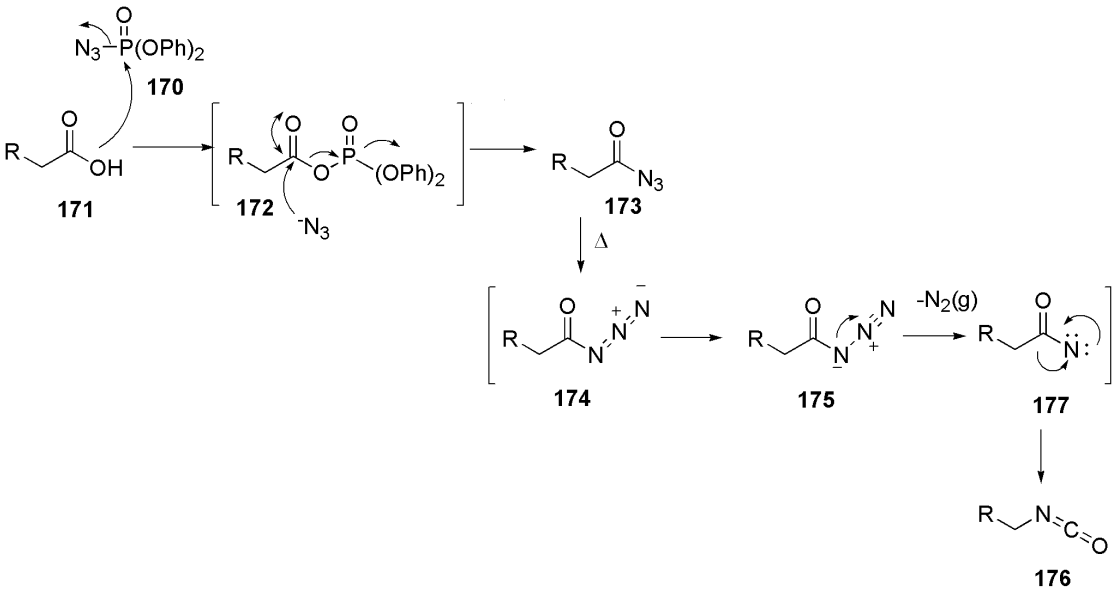
One additional cyclisation precursor that we were very interested in accessing was the piperonyl substrate **165k**. Our interest in this target stemmed from the frequent observation of the piperonyl motif in biologically active natural products based on the phenanthridine core (**Figure 1.15**), and thus we were keen to include this in our DOS library. An alternative route to this substrate was developed as we initially had concerns over the stability of the piperonyl bridge toward the $LiAlH_4$ used in the standard amine synthesis (**Table 3.2**).[γ] We proposed to synthesise the cyclisation precursor **165k** from Boc-protected piperonyl analogue **168k** as previously shown, but this time synthesis of the latter substrate would be obtained directly from acid **169k** via a Curtius rearrangement. (**Scheme 3.3**).

[γ] Subsequent to our investigation we have discovered two examples of the methylenedioxy bridge surviving both $LiAlH_4$ and DIBAL reductive conditions respectively.[109,110]



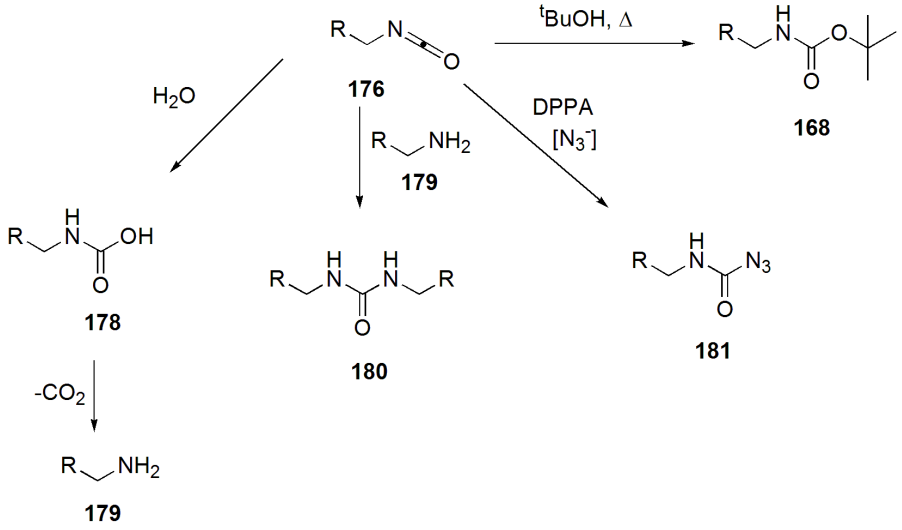

**Scheme 3.3** *Retrosynthetic analysis for piperonyl cyclisation precursor **165k**.*

The Curtius rearrangement in general involves three major steps, the first of which is diphenylphosphorylazide (dppa) **170** promoted conversion of an acid **171** into its corresponding acyl azide **173** (**Scheme 3.4**).[111] The second step involves thermal decomposition of the azide, with release of $N_2$ to afford an isocyanate **176**, via an acyl nitrene intermediate **177**.[112]




**Scheme 3.4** *The Curtius rearrangement.*

The final step involves the highly electrophillic carbon of the isocyanate,[112] that can be trapped with a nucleophile to afford a variety of products, both desired and undesired (**Scheme 3.5**). For our purposes, $^{t}$BuOH was used as the nucleophile as this permitted direct access to the desired Boc species **168k**, but the reaction can be carried out in the presence of water to afford the corresponding amine **179**.[113] Commonly two side products are observed, namely the urea **180** or the carbamoyl azide **181**, formed from nucleophillic attack of the isocyanate by the amine or residual $^{-}N_3$ respectively.[112]

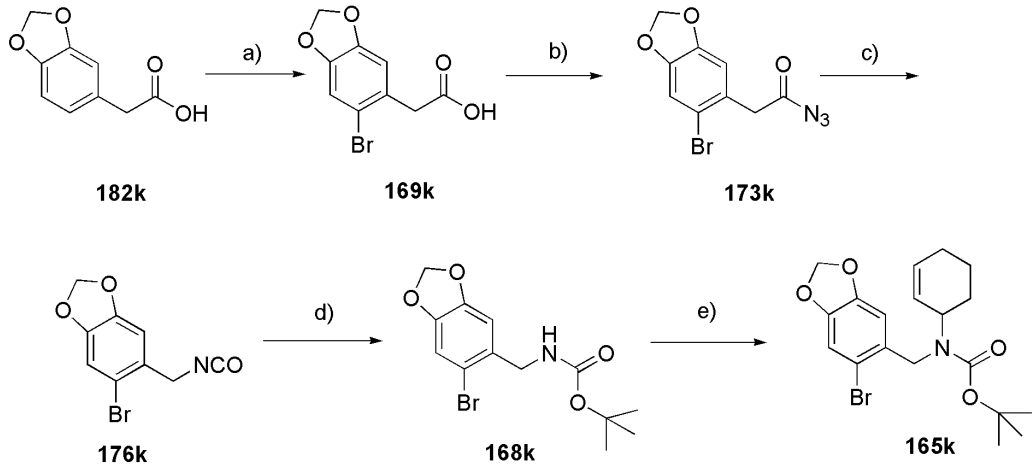



**Scheme 3.5** *Potential products from nucleophillic attack at the isocyanate.*

Our first job was to synthesise the 2-bromo-homopiperonylic acid starting material in order that we could trial the Curtius rearrangement. We did this by treatment of commercially available homopiperonylic acid **182k** with DBDMH (1,3-dibromo-5,5-dimethylhydantoin) under aqueous conditions which we found to be far superior to NBS under aqueous or DMF conditions (**Scheme 3.6**).[114]

We had previously trialled some one-pot[115,116] variants of the Curtius reaction on the homopiperonylic acid, resulting in low yields (<23%) and a significant amount of urea **180k** and carbamoyl azide **181k** side products being observed (**Scheme 3.5**, R=piperonyl). This led us to choose a two-pot modified Curtius reaction for the reaction of 2-bromo-homopiperonylic acid **169k**, where the isocyanate intermediate was isolated.[117]

Following these two-phase Curtius conditions we discovered that acyl azide **173k** underwent partial conversion to isocyanate **176k** upon purification through a silica plug. We could find no previous reports of this occurring in the literature where conversion to the isocyanate always requires heating conditions. However, one study examining the thermally-induced Curtius rearrangement of *ortho*-alkyl benzoyl azides, reported large rate-accelerations for these substrates as compared to their *ortho*-unsubstituted counterparts.[118] The facile decomposition of acyl azide **173k** to the corresponding isocyanate **176k** on silica could therefore be due to a similar effect.




**Scheme 3.6** *Synthesis of piperonyl cyclisation precursor **165k**.*

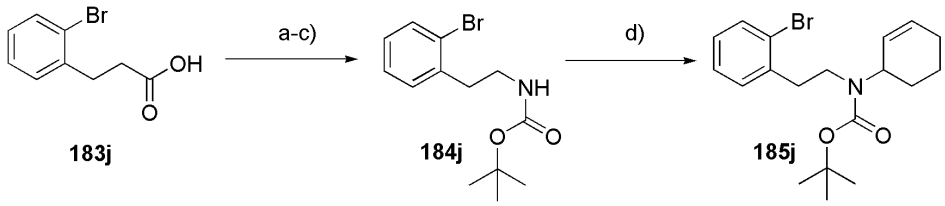
a) DBDMH, 4 M NaOH, $H_2O$, r.t., 16 h, 91%; b) dppa, $Et_3N$, $CH_2Cl_2$, 0 °C → r.t., 0.5 h; c) i) silica plug filtration (partial conversion); ii) PhMe, 110 °C, 1 h (total conversion); d) $^t$BuOH, 80 °C, 16 h, 50% over 3 steps; e) NaH, 3-bromocyclohexene, DMF, 0 °C- r.t., 16 h, 75%.

Total conversion to the isocyanate **176k** was achieved after refluxing in toluene for 1 h, and subsequent treatment of the isocyanate with $^t$BuOH led to the formation of the desired Boc-analogue **168k** in 50% yield over the three steps. Residual urea and carbamoyl azide by-products **180k** and **181k** were isolated from the product mixture, and identified by their carbonyl IR peaks (1579 $cm^{-1}$ and 2156 $cm^{-1}$ respectively). Subsequent alkylation of **168k** under standard conditions afforded cyclisation precursor **165k** in 75% yield.

This Curtius approach clearly offers a comparably yielding and milder route to the synthesis of the desired Boc-protected amine analogues, with the advantage of essentially two main steps as compared to four using the standard route (**Table 3.2** and **3.4**). While we were very pleased with its successful application to the piperonyl analogue, our alternative route to the other substrates was more than satisfactory, and a lack of commercial availability of other homo benzoic acid starting materials meant we did not apply the conditions to any of our other benzyl substrates.

### 3.2.5 Phenethyl substrate via Curtius rearrangement

However, we did apply the Curtius conditions to the synthesis of substrate **184j**, since we had experienced problems accessing this analogue using the standard route, and the starting material 3-(2-bromophenyl)propionic acid **183j** was commercially available (**Scheme 3.7**). We were delighted to discover that the desired carbamate product **184j** was obtained in 77% yield, offering a marked improvement over the 3-step standard synthesis (see **Chapter 6** for details).




**183j** **184j** **185j**

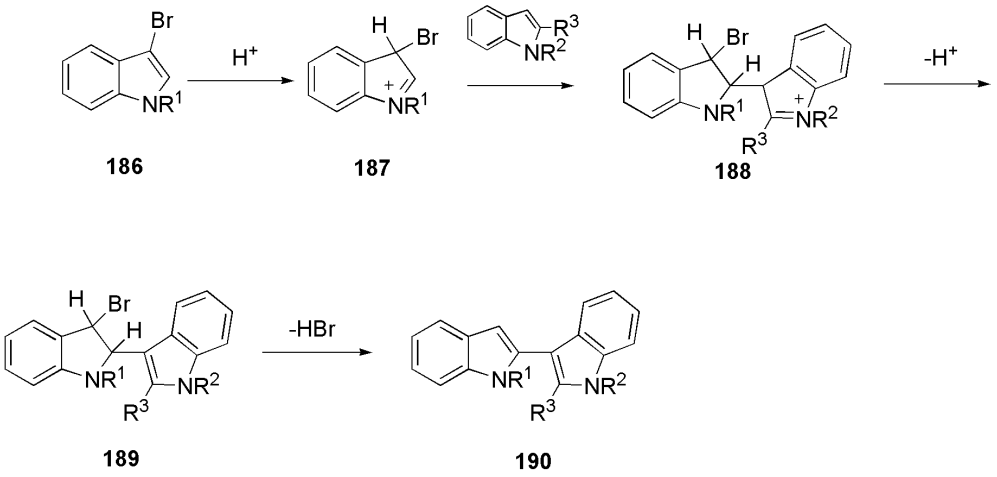
**Scheme 3.7** *Curtius rearrangement to afford phenethyl substrate **184j**.*

a) i) dppa, $Et_3N$, $CH_2Cl_2$, 0 $^oC$ – r.t., 0.5 h; ii) silica plug filtration (partial conversion); b) PhMe, 110 $^oC$, 1 h (total conversion); c) $^tBuOH$, 80 $^oC$, 16 h, 77% over 3 steps; d) NaH, 3-bromocyclohexene, DMF, 0 $^oC$- r.t., 16 h, 45%.

Unfortunately however, the final alkylation step to afford cyclisation precursor **185j** only proceeded in 45% yield, and we were not able to improve upon this using the TBAI/$Cs_2CO_3$ protocol developed by Salvatore *et al.* for the *N*-alkylation of carbamates.[119,120] The limitations of this step resulted in insufficient quantities of phenethyl analogue **185j** for a satisfactory study of the Heck reaction. While it was clear from the initial studies that cyclisation occurred to a significant extent, identification of the complex mixture of isomeric products obtained, even under cationic conditions made the evaluation of this cyclisation a difficult task.

### 3.2.6 Issues with indoles

We experienced difficulty accessing the desired indole amine buiding block **164h**. Following the $LiAlH_4$ reduction step in our standard synthetic sequence (**Table 3.2**), treatment of the free amine with HCl in $Et_2O$ led to a complex mixture visible by $^1H$ NMR. Although we were confident that a significant proportion was the desired bromoindoleamine **164h**, we were intrigued as to the identity of the minor product(s). We initially considered the formation of an indole-dimer species since 3-bromoindoles have been reported to undergo dimerisation under acidic conditions.[121] The driving force for such a reaction is the loss of HBr which enables rearomatisation and formation of the 2,3-linked indole dimer (**Scheme 3.8**).



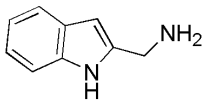

**Scheme 3.8** *Synthesis of dimeric indole species.*[121]

$R^1$=H, Me; $R^2$=H, Me, Bn; $R^3$=H, Me, Ph.

However, this rearomatisation step was clearly not possible for our substrate due to the additional methylamine substituent at the 2-position of bromoindoleamine **164h**. Additionally, no evidence for the presence of such a dimer was visible in the mass spectrum.

An extra singlet in the $^1H$ NMR spectrum at 6.26 ppm (in DMSO) led us to consider that one of the products was the debrominated indole amine **191** (**Figure 3.3**). Additionally, we observed the correct mass for this (*m/z* 146) in the mass spectrum of the mixture. Further evidence for the presence of this product was obtained when following a resynthesis, we purified the reaction mixture by flash chromatography on

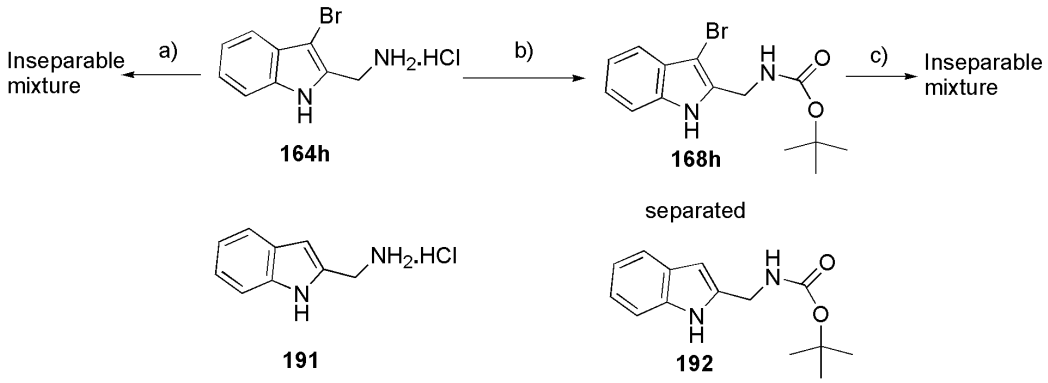
silica, rather than by HCl salt formation. Although the majority of the reaction mixture appeared to decompose on the silica, the only isolated product was a trace amount of debrominated indole amine **191** (**Figure 3.3**), which we confirmed by comparison of its $^1$H NMR spectrum with that of the literature.[122] We therefore proposed that **191** was formed during the $LiAlH_4$ reduction step, and that the hydrochloride salt of **191** was the minor contaminant in our product mixture. We propose that the remainder of the unassigned signals in the $^1$H NMR spectrum resulted from incomplete formation of the HCl salt of bromo-indole amine **164h**.




**191**

**Figure 3.3** *De-brominated indole* **191**.[122]

We continued our studies towards indole cyclisation precursor **165h** using the indole-amine hydrochloride mixture. After conversion of the amine hydrochloride salts to the free amines, coupling with 3-bromocyclohexene under standard conditions gave an inseparable mixture of products (**Scheme 3.9**), perhaps not surprising when mono- and dialkylation can occur for both the indole amine species.



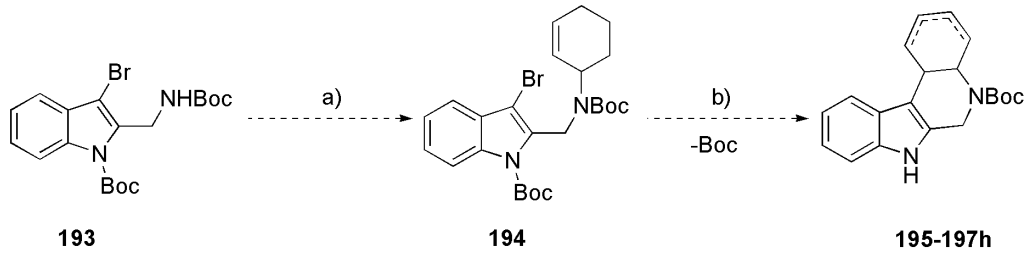

**Scheme 3.9** *Attempted synthesis of indole cyclisation precursor.*

a) $^i$Pr$_2$NEt, 3-bromocyclohexene, MeCN, 16 h, r.t.; b) $Boc_2O$, $Et_3N$, $CH_2Cl_2$, r.t., 16 h, **168h** 49%, **192** 24%; c) NaH, 3-bromocyclohexene, DMF, 0 $^o$C → r.t., 16 h.

We therefore tried Boc-protecting the amine first, which had proved a successful method of circumventing the dialkylation issue previously. This gave excellent

conversion to a mixture of bromo-carbamate **168h** and carbamate **192**, and permitted us to separate the two compounds. In contrast to an example in the literature,[123] we observed no Boc-protection of the indole nitrogen, which we have attributed to using less equivalents of $Boc_2O$ in our case (2 eq vs 5 eq).

Simple deprotonation of Boc-indole **168h** with NaH, and attempted alkylation with 3-bromocyclohexene led, not surprisingly, to a complex mixture of products due to concomitant deprotonation/alkylation of the indole N-H. As a result we could not isolate any of the desired cyclisation precursor from the complex product mixture following the alkylation reaction. In light of the numerous setbacks we had encountered during the attempted synthesis of **165h**, we chose not to pursue the synthesis of this analogue any further. If the synthesis was to be repeated in future studies, it would be favourable to Boc-protect the indole nitrogen and the amine at the same time, or even Boc-protect the indole nitrogen at an earlier stage in the synthesis. Although Boc-indoles are less susceptible than Boc-amines to acidic deprotection conditions, they can be selectively removed under thermolysis at 130 °C in DMSO.[124] The Heck cyclisation conditions at 140 °C would therefore most likely facilitate deprotection of the Boc-indole (**Scheme 3.10**).



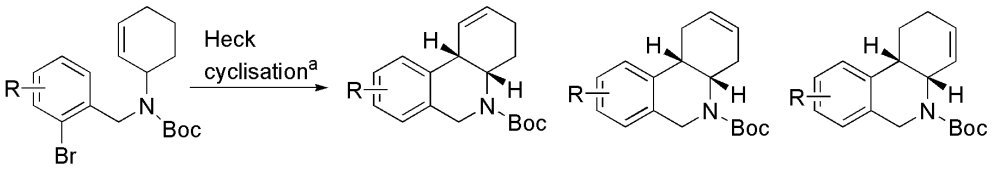

**Scheme 3.10** *Alternative synthesis of indole analogue.*

a) NaH, 3-bromocyclohexene, DMF, 0 °C → r.t.; b) Palladacycle **100** (5 mol%), $Ag_2CO_3$ (1 eq) or $MeNCy_2$ (4 eq), DMF, 140 °C.

### 3.2.7 Heck cyclisation of aryl/heteroaryl cyclisation precursors

With our cyclisation precursors **165a-f**,**k** in hand we studied their reaction under both our cationic and neutral palladacycle **100** catalysed conditions.

**Table 3.5** *Cationic cyclisation of aryl/heteroaryl cyclisation precursors* ***165a-f,k.***




**165a-f,k** **195a-f,k** **196a-f,k** **197a-f,k**

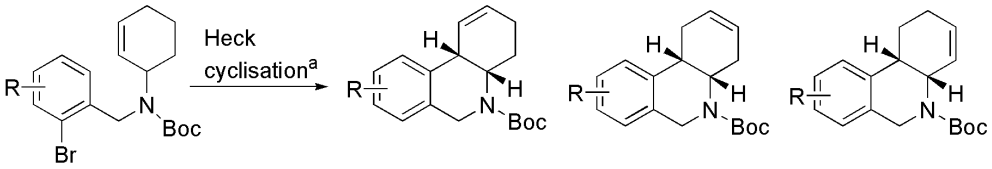
| Entry | 165 | Substrate (R= ) | t (h) (%) | Yield 195-197 (%) | Ratio[b] 195:196:197 |
|---|---|---|---|---|---|
| 1 | **94b** | H | 2 | 99 | 83:15:2 |
| 2 | a | 4-Me | 2 | 99 | 78:17:5 |
| 3 | b | 4-F | 2.5 | 99 | 81:14:5 |
| 4 | c | 5-MeO | 4 | 99 | 77:19:4 |
| 5 | d | 4,5-diMeO | 1 | 99 | 84:13:3 |
| 6 | e | [*Naphthyl*][$] | 4 | 88 | 81:14:5 |
| 7 | f | [*Thiophene*][$] | 3 | 99 | 64:21:15[c] |
| 8 | k | [*Piperonyl*][$*] | 2 | 70 | 76:18:6 |

[a] Conditions: aryl halide (1 eq), palladacycle **100** (5 mol%), $Ag_2CO_3$ (1 eq), DMF, 140 °C. [b] Ratio identified from $^1$H NMR of pure product mixture. [c] Traces of minor diastereomer peaks visible in the $^1$H NMR. [$] See footnote **Table 3.2**. * As in **Scheme 3.6**.

The cyclisation of all our substrates **165a-f,k** was found to proceed rapidly and efficiently in all cases, although a slight loss in conversion was observed with the piperonyl analogue **165k** which was surprising given the excellent reactivity of the 4,5-dimethoxy analogue. Identification of the isomer ratio was achieved by integration of the respective $^1$H NMR signals (as illustrated in **Chapter 2.5.1**). As expected, the $\Delta^{1,2}$ isomer was obtained as the major product from the cyclisation of all the analogues, with a comparable ratio to the cationic cyclisation of standard Boc substrate **94b** (entry **1**). Interestingly, three minor peaks were observed between 3.00 and 4.00 ppm in the $^1$H NMR spectra of the thiophene product mixture **195-197f** where the NCHC*H* proton is usually observed (proton 'h', **Figure 2.4**, **Chapter 2**). This suggests the possible formation of trace amounts of the *trans*-ring junction diastereomer, although reaction scale did not permit us to isolate any such product.

The application of our neutral Heck cyclisation conditions was also applied to substrates **165a-f,k** as reported in **Table 3.6**.

**Table 3.6** *Neutral cyclisation of aryl/heteroaryl cyclisation precursors* ***165a-f,k***.




**165a-f,k** **195a-f,k** **196a-f,k** **197a-f,k**

| Entry | 165 | Substrate (R= ) | t (h) (%) | Yield 195-197 (%) | Ratio[b] 195:196:197 |
|---|---|---|---|---|---|
| 1 | **94b** | H | 3 | 95 | 36:38:26 |
| 2 | a | 4-Me | 12 | 76 | 26:57:17 |
| 3 | b | 4-F | 5 | 72 | 27:44:29 |
| 4 | c | 5-MeO | 6 | 73 | 36:44:20 |
| 5 | d | 4,5-MeO | 12 | 75 | 41:32:27 |
| 6 | e | [*Naphthyl*][$] | 5 | 74 | 42:42:16 |
| 7 | f | [*Thiophene*][$] | 5 | 79 | 18:34:30:(18)[c] |
| 8 | k | [*Piperonyl*][$*] | 24 | 59 (32)[d] | 41:26:33 |
| 9 | k | [*Piperonyl*][$*] | 18[e] | 80 (11)[f] | 18:46:36 |
| 10 | k | [*Piperonyl*][$*] | 18 | 99[g] | 39:37:24 |

[a] Conditions: aryl halide (1 eq), $MeNCy_2$ (4 eq), palladacycle **100** (5 mol%), DMF, 140 °C. [b] Ratio identified from $^1$H NMR of pure product mixture. [c] Quantifiable minor diastereomer peaks visible in the $^1$H NMR (7:11). [d] 32% dehalogenated product **198k** recovered (see **Chapter 6**). [e] $Pd_2(dba)_3$ (5 mol%), $^t$$Bu_3PHBF_4$ (10 mol%), $MeNCy_2$ (4 eq), MeCN, r.t. [f] Starting material recovered. [g] as entry **9** but at 50 °C. [$] See footnote **Table 3.2**. * As in **Scheme 3.6**.

We found that for the majority of our substrates, the standard neutral palladacycle catalysed reaction conditions promoted cyclisation to the expected mixture of isomer products **195-197**. However, conversions were lower in all cases than that exhibited by standard Boc substrate **94b** (95% in 3 h), and reaction times were longer, especially with the electron rich aromatics (entries **2**, **4**, **5**, **8**) where clearly the oxidative addition step will be less favoured. For piperonyl substrate **165k** (entry **8**) a significant amount of the dehalogenated product **198k** was recovered indicating the presence of Pd black (see **section 2.3.4**). This provides strong evidence for the reluctance of this substrate to undergo oxidative addition, since from our experience, Pd black is only formed from palladacycle **100** as a result of its standard deactivation

pathway, i.e near the end of the catalyst's lifetime. Fortunately, application of our low temperature ($^{t}Bu_3P)_2Pd$ conditions (entry **9**) enabled the recovery of the desired product mixture **195k**-**197k** in 80% yield at r.t, and 99% yield at 50 $^{o}C$ (entry **10**).

For the cyclisation of thiophene **165f** we again observed traces of what we propose to be the *trans*-ring junction minor diastereomers. For the cyclisation of sulfonamide protected thiophene analogue **157** (**section 3.2.1**) under both neutral and cationic conditions, no trace of such a product was observed. Additionally, no similar product peaks have been observed in the $^{1}H$ NMR spectra for the cyclisation of any of the other Boc-protected analogues. The formation of such a product is therefore unique to the combination of the thiophene and the Boc-protecting group.

We propose that some form of chelation between the thiophene sulfur and the carbonyl of the Boc protecting group enables the cyclisation precursor to become locked in a conformation that allows subsequent formation of the *trans*-ring junction phenanthridine. However, due to the small scale of the reaction, we have not isolated any of the minor products and therefore do not have proof of this hypothesis. Additionally, a literature search for similar thiophene carbamates has not highlighted any similar reaction abnormalities.

### 3.3 Stereochemical Diversity

There are many bioactive phenanthridine natural products that have hydroxylated or polyhydroxylated C-rings (**Figure 3.4**).[125] A sensible direction toward converting our aryl phenanthridine analogues into a DOS library would therefore be dihydroxylation or epoxidation of the alkene bond to introduce an element of stereochemical diversity.

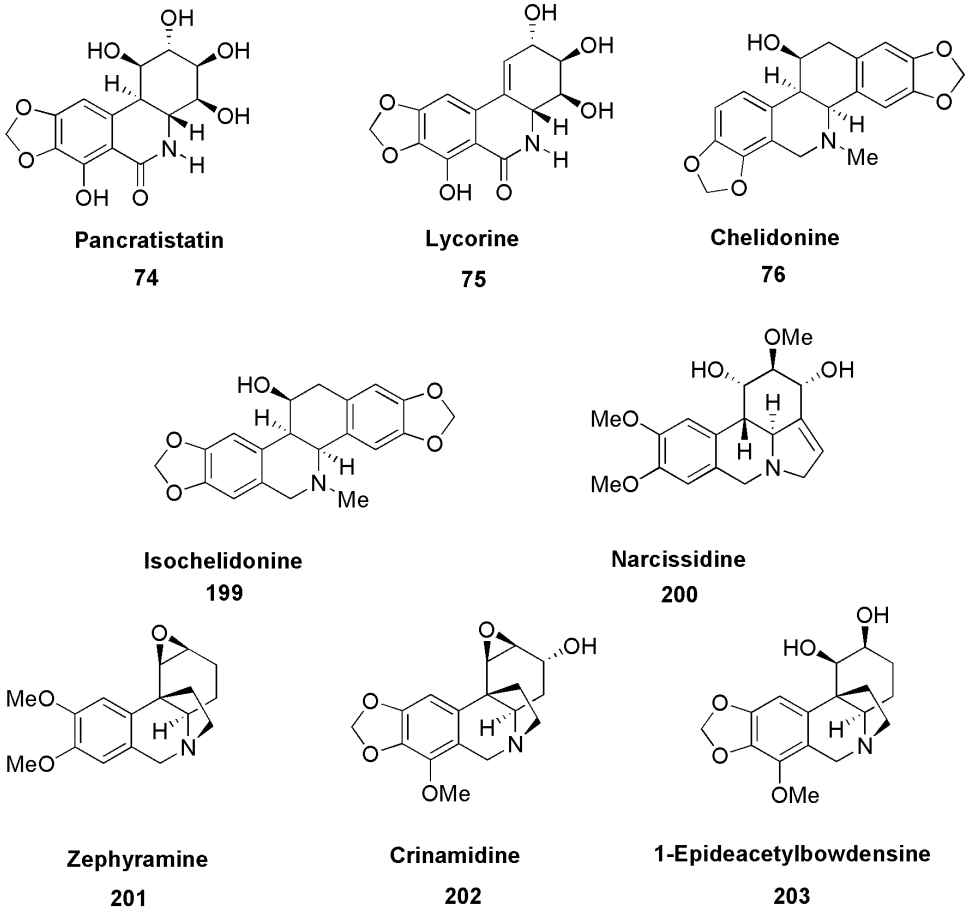
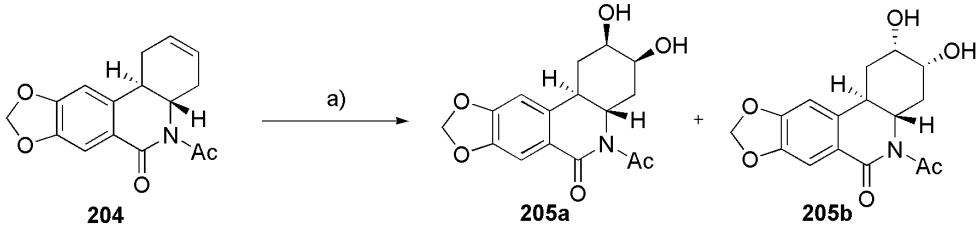



**Figure 3.4** *Hydroxylated C-ring phenanthridine natural products.*[125]

### 3.3.1 *Cis*-dihydroxylation

Conditions for the *cis*-dihydroxylation of *trans*-ring junction phenanthridine **204**, were reported in the literature, affording diasteromeric diol-products **205a** and **206b** in excellent yield (**Scheme 3.11**).[126]




**Scheme 3.11** *Literature conditions for cis-dihydroxylation.*[126]

a) $OsO_4$, NMO, THF/$H_2O$, r.t., 18 h, 84%, dr 1:1.

*Trans*-ring junction phenanthridines sit in a flat conformation in 3D space, so the diasteromeric ratio of 1:1 is hardly surprising, since both faces of the C-ring are equally accessible by the $OsO_4$ reagent (**Figure 3.5**). In contrast, *cis*-ring junction phenanthridines occupy a more cupped conformation, rendering the convex face more favourable for dihydroxylation, potentially resulting in high diastereomeric ratio (**Figure 3.6**).

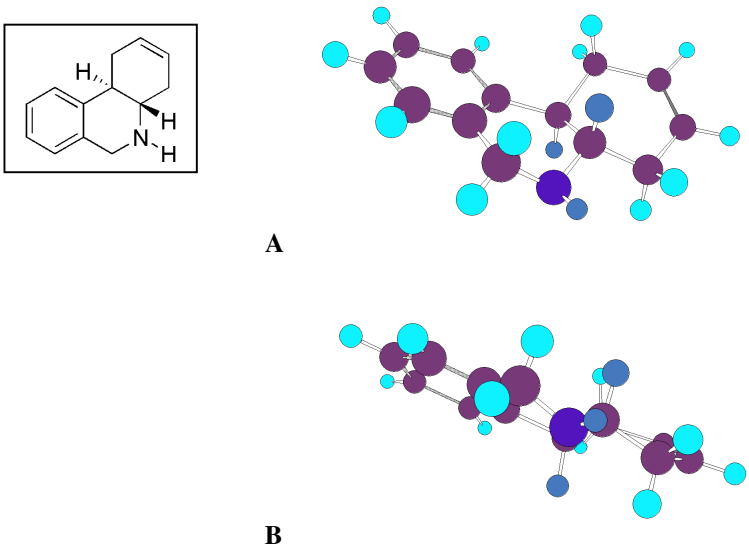



**Figure 3.5** *3D models of a typical trans ring junction phenanthridine.*

Angle **A** illustrating the full molecule. Angle **B** illustrating the lat planar conformation of molecule.

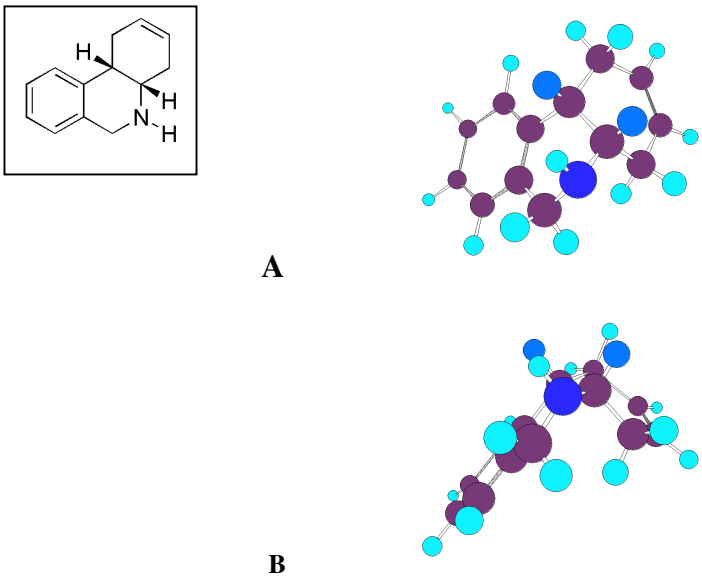
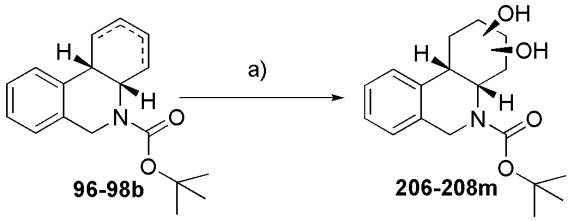



**Figure 3.6** *3D models of a typical cis ring junction phenanthridine.*

Angle **A** illustrating the full molecule. Angle **B** illustrating the cupped conformation of molecule.

The reaction was tested on all three isolated double bond isomers **96-98b** and we observed high conversions and diastereomeric ratios (>83:17) for the *exo*-syn product across all substrates (**Table 3.7**).

**Table 3.7** *Dihydroxylation test reactions.*




| Entry | Substrate | Product | Yield (%) | dr[a] |
|---|---|---|---|---|
| 1 | **96b** ($\Delta^{1,2}$) | **206m** ($\Delta^{1,2}$) | 99 | 83:17 |
| 2 | **97b** ($\Delta^{2,3}$) | **207m** ($\Delta^{2,3}$) | 99 | 85:15 |
| 3 | **98b** ($\Delta^{3,4}$) | **208m** ($\Delta^{3,4}$) | 99 | 85:15 |

a) $OsO_4$, NMO, THF/$H_2O$, r.t., 18 h. [a] Diastereomeric ratio determined by integration of the relevent peaks in the $^1H$ NMR spectrum.

### 3.3.2 Proof of stereochemistry

We were confident from the molecular models we had studied that the major product would have the hydroxyl groups on the exo-face, however confirmation was required. During the application of this methodology to the DOS library synthesis (**Chapter 4**) we isolated both the $\Delta^{2,3}$ piperonyl analogue *cis*-dihydroxyl products **207k** and **209k** and studied them using 2D nOESY NMR. For the major product, strong nOE's were observed between the two ring junction protons, and between the two C*H*OH protons, but there were no cross peaks between the two sets which is indicative of structure **207k** (**Figure 3.7**). For the minor product, again strong nOE's were observed between the two ring junction protons, and between the two C*H*OH protons, but this time an additional cross peak was observed between one of the ring junction protons and one of the C*H*OH protons (**Figure 3.8**). This would be true for the minor product where these two sets of protons are on the same face of the phenanthridine.

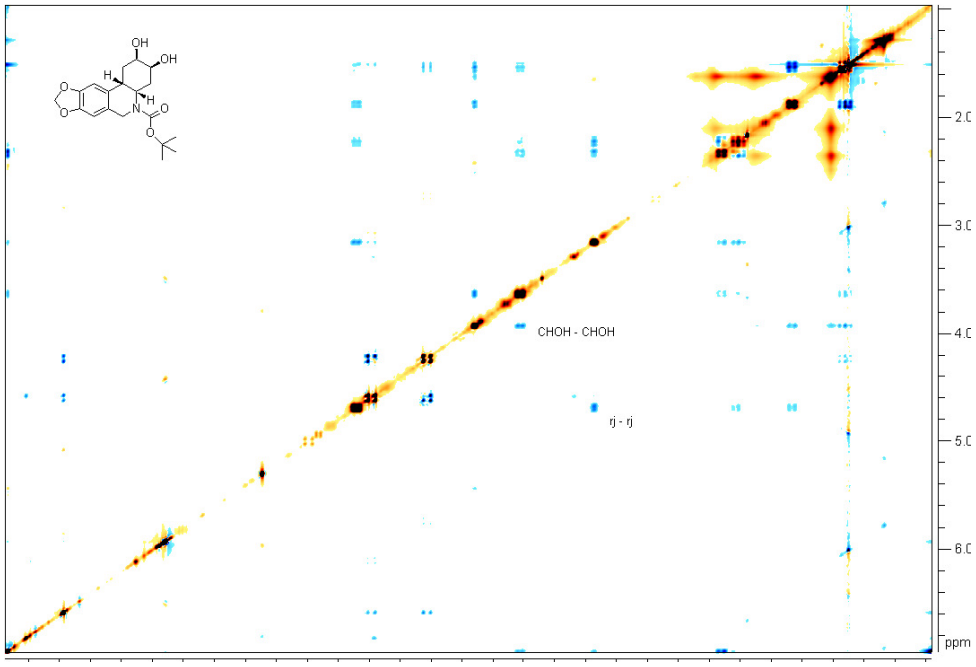



**Figure 3.7** *2D nOESY NMR for major exo-syn diol product* ***207k*** *illustrating a lack of ring junction (rj) to CHOH cross peaks.*

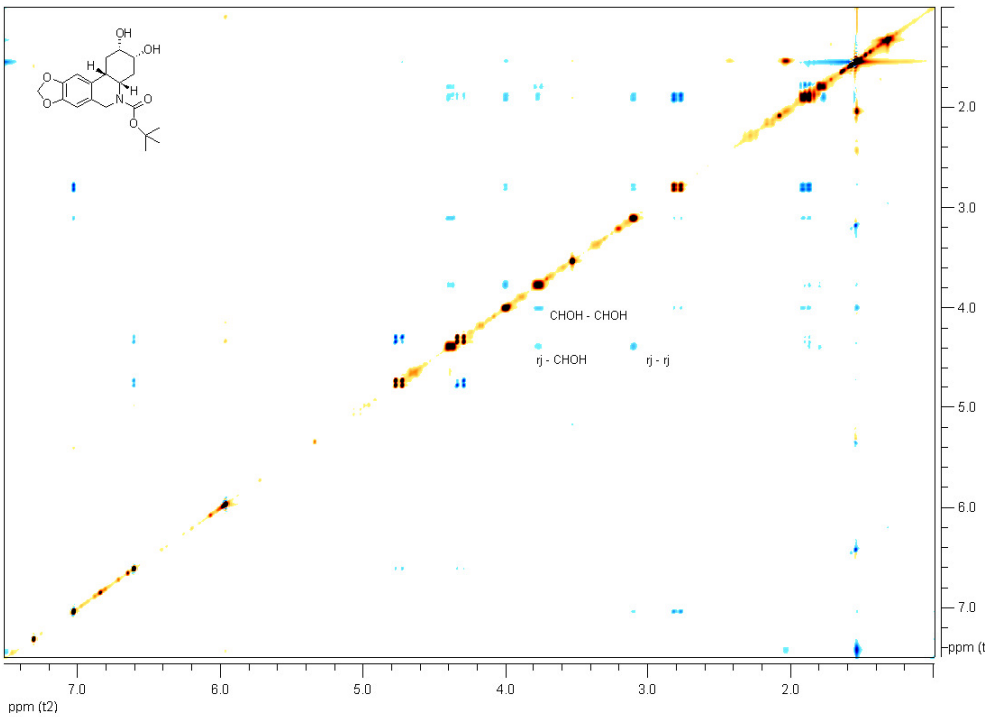
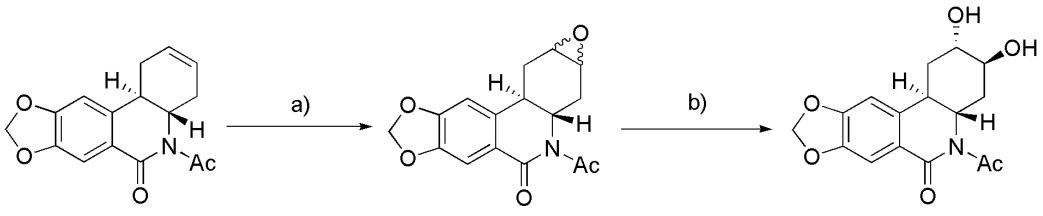



**Figure 3.8** *2D nOESY NMR for minor endo-syn diol product* ***209k*** *illustrating a ring junction (rj) to CHOH cross peak.*

### 3.3.3 Epoxidation using mCPBA or via a bromohydrin

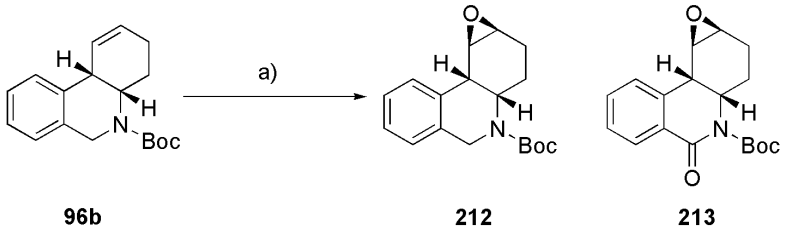
With conditions for the *cis*-dihydroxylation of our phenanthridines safely in hand, we looked toward developing conditions for accessing the *trans*-diol, via the epoxide intermediate using mCPBA-promoted conditions reported in the literature (**Scheme 3.12**.[126] Although a mixture of epoxides **210** was formed from the *trans*-ring-junction analogue **204**, we expected *exo*-selectivity for epoxidation of the *cis* analogue, due to the aforementioned cupped conformation adopted by the substrate.




**Scheme 3.12** *Literature conditions for trans-diol formation via the epoxide.*[126]

a) mCPBA, $CH_2Cl_2$, r.t., 18 h, 73%; b) $HClO_4$, $H_2O$/THF, r.t., 1.5 h, 64%.

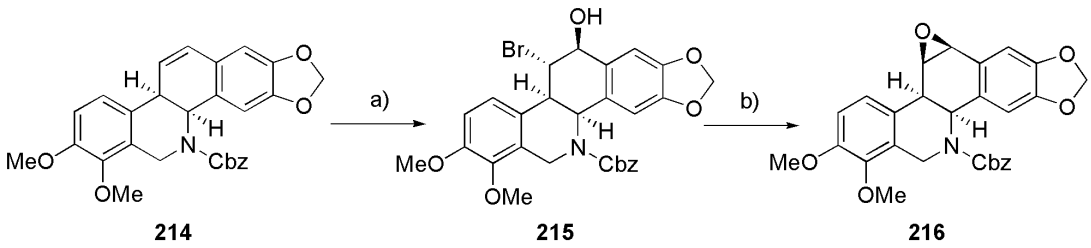
Application of these conditions to alkene **96b** led to the formation of desired epoxide **212**, along with the corresponding phenanthridone epoxide **213** (**Scheme 3.13**). Lowering the temperature (0 °C) or reducing reaction time (3 h) offered no improvement. The benzylic position of the phenanthridine is known to be susceptible to oxidation under mCPBA conditions,[127] and a postulated mechanism involves H-atom abstraction, followed by benzylic radical trapping by air.[128]




**Scheme 3.13** *Epoxidation using mCPBA.*

a) mCPBA, $CH_2Cl_2$, 16 h, r.t., 99% **212**:**213** 59:43; 0 °C, 16 h, 0%; r.t., 3 h, 50% **212**:**213** 1:1.

An alternative approach for the epoxidation of alkenes involves a two-step sequence via an intermediate bromohydrin **215**. This method was successfully applied in the synthesis of (+)-homochelidonine where prevention of benzylic oxidation was essential (**Scheme 3.14**).[129]




**Scheme 3.14** *Bromohydrin formation in the synthesis of (+)-homochelidonine.*[129]

a) NBS, THF/$H_2O$, r.t., 1.5 h, 75%; b) KO$^t$Bu, THF, -78 °C, 0.5 h, 99%.

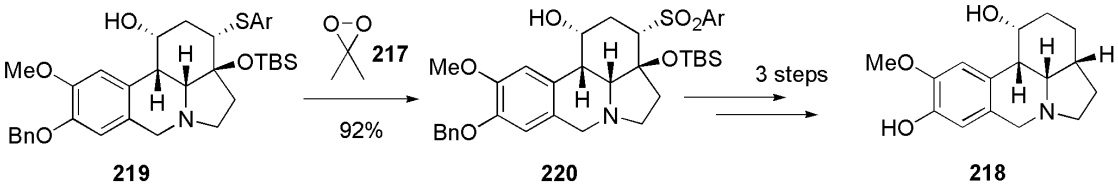
Unfortunately application of the bromohydrin formation conditions to our Boc alkene **96b** resulted in the formation of multiple products along with considerable starting material. The formation of up to four bromohydrins was expected as the bromonium ion intermediate can form on either face of the alkene (although we would expect the *exo* to be favoured), and can then open up in either direction. We propose that the cupped nature of the *cis*-ring junction phenanthridine hindered both the formation of the bromohydrin on the concave face, and the opening of the *exo*-

bromohydrin by attack of $H_2O$ from the concave face leading to the large amount of alkene **96b** being recovered.

### 3.3.4 Epoxidation using DMDO (dimethyldioxirane)

Another alternative reagent for the preparation of epoxides from alkenes is DMDO **217** (**Scheme 3.15**), an oxidising agent derived from acetone.[130] DMDO has been found to be both a mild and efficient reagent, with the added advantage that only acetone is produced as a by-product in the reaction. Although it is highly selective for alkenes, it is also capable of oxidising several other functional groups including primary amines to nitro compounds[131] and sulfides to sulfoxides.[132]

We were keen to explore the use DMDO for the epoxidation of our substrate after a recent report where the reagent was successfully applied to the synthesis of phenanthridine natural product fortucine **218**.[132] In this example DMDO was used to successfully oxidise sulphide **219** to sulfone **220**, with no oxidation occurring at the benzylic position as we had observed with mCPBA.




**Scheme 3.15** *Application of DMDO in the synthesis of (±) Fortucine **218**.*[132]

Although DMDO is a very well known reagent, it is very unstable and therefore not commercially available. To generate the reagent, a fresh solution must be prepared from oxone, sodium bicarbonate and acetone using a complex set-up of glassware under vacuum (**Figure 3.9**).[133] The preparation of DMDO is known to be rather inefficient, typically yielding a solution of <0.15 M in acetone. Several factors account for this low concentration including a large number of possible side reactions,[134] and inefficient collection of the dioxirane reagent in the cold trap.

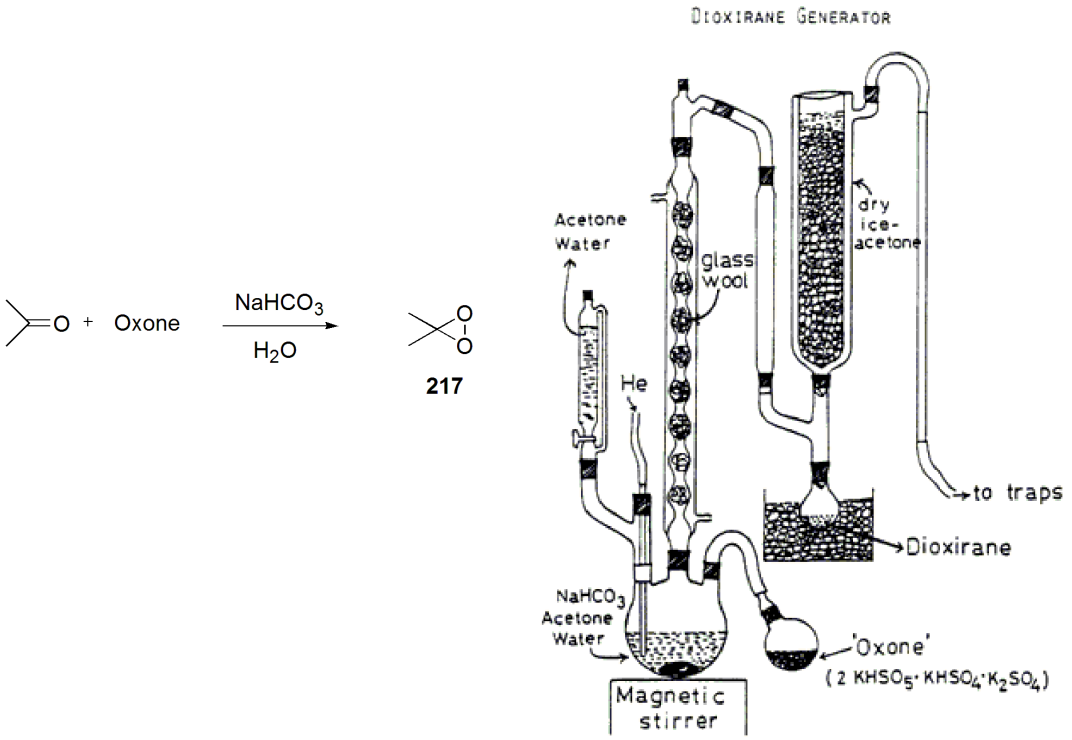
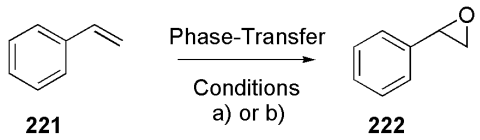



**Figure 3.9** Apparatus for the preparation of DMDO **217** from acetone.

Diagram reproduced from the original Organic Syntheses preparation.[133]

In agreement with the literature precedent, we also found the preparation of DMDO to be extremely inefficient, even after careful repetition a number of times. Although the solution concentration was not measured,[133] we found that the reaction of just 80 µmol of alkene with 10 ml of DMDO solution, gave <30% conversion to the epoxide, suggesting a concentration of just 0.003 M. Although the conversion was poor, no trace of phenanthridone epoxide **213** was observed in the product mixture suggesting a more efficient preparation of DMDO would provide the solution to achieving selective epoxidation.

There have been a number of reports of the *in situ* generation of the reagent under phase-transfer conditions.[131,135] We trialled these conditions for the epoxidation of styrene **221** in order to determine if they would be successful (**Scheme 3.16**).




**Scheme 3.16** *In situ generation of dioxirane.*[131]

a) oxone, $Me_2O$, $CH_2Cl_2$, $Na_2HPO_4$ aq. buffer, $n$Bu$_4$NHSO$_4$, pH 7.5-8, 0 $^oC$, 3 h, 20%; b) oxone, $(CF_3)_2O$, $CH_2Cl_2$, $Na_2HPO_4$ aq. buffer, $n$Bu$_4$NHSO$_4$, pH 7.5-8, r.t., 4 h, 20%;

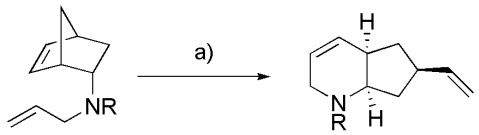
The conditions for *in situ* generation of the DMDO, though simpler than the traditional method, were still complex, requiring careful monitoring of the pH to avoid possible decomposition of the dioxirane at pH>8. Despite our care, we were not able to satisfactorily reproduce these conditions and only 20% conversion was observed at 0 $^oC$. In an attempt to reduce the electron density of the O-O bond and therefore generate a more reactive dioxirane, we switched acetone for trifluoromethylacetone.[134] However again, only a 20% epoxide was obtained, even after raising the reaction temperature from 0 $^oC$ to r.t.

Our studies into the application of DMDO showed that the reagent is selective for epoxidation without oxidation at the benzylic position to give the phenanthridone **212**. However, we were not able to satisfactorily replicate the literature methods for traditional or *in situ* generation of the dioxirane. After numerous unsuccessful attempts to obtain selective epoxidation, we stopped all investigations into the synthesis of epoxides to focus on other areas of the project.

## 3.4 Skeletal Diversity

### 3.4.1 Ring-rearrangement metathesis (RRM)

Olefin metathesis has now become a well-established tool in organic synthesis. Originally ring-closing metathesis (RCM) formed the basis of much of the research in this field, but more recent efforts have included the development of protocols to facilitate ring-opening metathesis (ROM) and cross-metathesis reactions.[136] Domino metathesis or ring-rearrangement metathesis reactions (RRM), involving combinations of these metathesis protocols have also been reported, and implemented successfully in complex molecule synthesis.[137] These reactions involve intramolecular metathesis between an endocyclic olefin and a tethered exocyclic C=C or C≡C bond, in such a way that one ring is opening in a ROM process and another is formed in a RCM process (**Scheme 3.17**).[138]




**223** **224**

**Scheme 3.17** *RRM of 2-aminonorbornenes.*[138]

a) Grubbs I (10 mol%), ethylene, $CH_2Cl_2$, r.t., 16 h. R= Boc 90%; R= Cbz 90%; R= Ts 99%.

RRM has previously been used to prepare molecules with carbocyclic and oxocyclic skeletons,[139] but there are far fewer reports of its successful implementation in the synthesis of nitrogen containing systems.[140] Indeed, across the whole of metathesis chemistry, the presence of amino-functionality is rare (one example is illustrated above in **Scheme 3.17**).[138] The reason behind this lies in the ability of the amino group to coordinate to the transition metal of the metathesis catalyst, thus leading to deactivation and poor reactivity. Successful approaches to counteracting this problem include the use of Lewis acids to coordinate the amine;[141] the use of amines with strongly electron-withdrawing functionality (such as sulfonamides[142] or carbamates, **Scheme 3.17**); and the use of ammonium salts.[143]

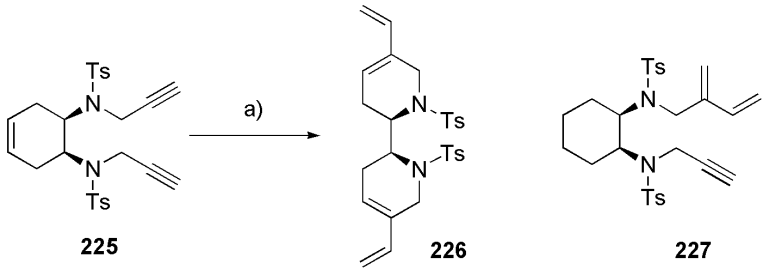
In the above example (**Scheme 3.17**), the cycloalkene **223** that undergoes ROM is a very highly strained norbornene. The drive to achieve a lower energy structural conformation makes norbornene units highly effective for ROM, and indeed most of

the successful examples of the RRM of amino-containing substrates use norbornene as the cycloalkene unit.[138] The majority of the other examples use cyclopentene[144-146] or cyclobutene[144] which both have more strained ring systems than cyclohexene and are thus pre-disposed to undergo ROM. To the best of our knowledge, only three successful examples of the ROM or RRM of unstrained cycloalkenes have been reported.

### 3.4.2 ROM/RRM of unstrained cycloalkenes

RRM of *bis*-propargyl-*N*-tosyl amine **225** was found to occur under Grubbs I or Grubbs II metathesis (**Table 3.8**).[142,147] However in this example the RRM only proceeded with low yields (<22%) and 1,3-diene **227** was recovered as the major product along with significant starting material. Formation of the 1,3-diene **227** occurs from the cross metathesis of the alkyne with ethylene and has been attributed to steric hindrance of the ruthenium catalyst at the reaction site.[146,148]

**Table 3.8** *Enyne metathesis of diyne **225**.*[142,147]

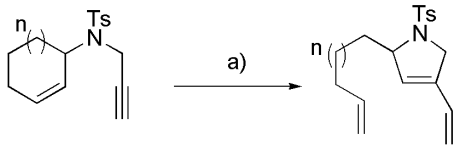



**225** **226** **227**

| Entry | Conditions[a] | T (°C) | t (h) | Conversion (%) | 226:227 |
|---|---|---|---|---|---|
| 1 | Grubbs I (5 mol%), $CH_2Cl_2$, $CH_2$=$CH_2$ | 25 | 20 | 63 | 1:5.3 |
| 2 | Grubbs I (10 mol%), $CH_2Cl_2$, $CH_2$=$CH_2$ | 25 | 20 | 79 | 1:3.9 |
| 3 | Grubbs I (10 mol%), $CH_2Cl_2$, $CH_2$=$CH_2$ | 50 | 20 | 61 | 1:2.6 |
| 4 | Grubbs II (10 mol%), PhMe, $CH_2$=$CH_2$ | 60 | 20 | 81 | 1:2.7 |

Interestingly, RRM of cycloalkene-ynes **228a-c** (**Table 3.9**),[146] was reported to proceed under similar conditions to those reported in **Table 3.8**, but this time excellent conversions to the pyrrolidine products **229a-c** was obtained in less than 4 hours at r.t. The 1,3-diene cross metathesis product was not observed though this could reasonably be attributed to the lack of steric congestion at the reaction site as opposed to *bis*-propargyl counterpart **225**. To the best of our knowledge, this example remains the highest yielding RRM of an unstrained cyclohexene.

**Table 3.9** *RRM of cycloalkene-ynes*.[146]

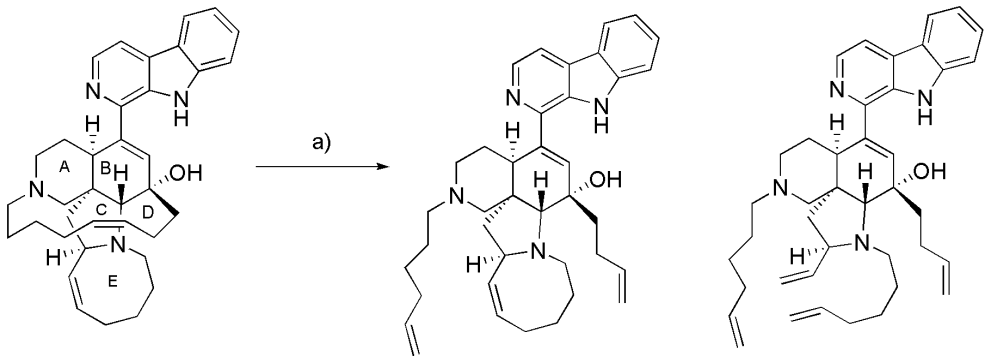



**228a-c** **229a-c**

| 228 | n | t (h) | Conversion (%) |
|---|---|---|---|
| a | 1 | 4 | 78 |
| b | 2 | 1 | 70 |
| c | 3 | 1 | 75 |

a) Grubbs I (10 mol%), ethylene, $CH_2Cl_2$, r.t.

One final example illustrates how ROM can be used in an elegant manner to generate biologically active compounds.[143] Exposure of the hydrochloride salt of Manzamine A **230** to Grubbs I under ethylene gave a 4:1 mixture of tetraene **231** and pentaene **232**, formed from ROM of the 13-membered D ring or the 8-membered E ring respectively (**Scheme 3.18**). The high conversion obtained for the ROM of these large-ring cycloalkenes shows the power that a simple reaction such as ROM has to generate diversity from a common starting material.



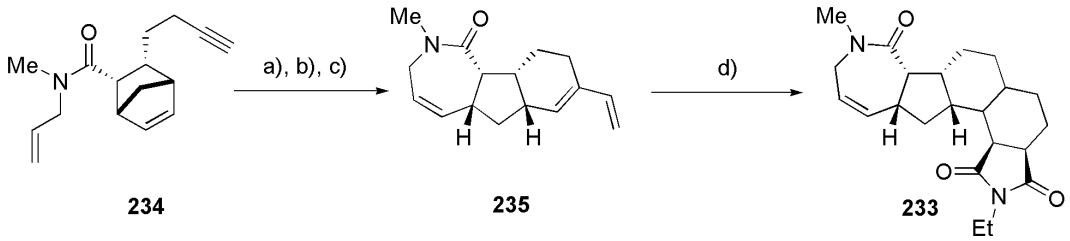

**230** **231** **232**

**Scheme 3.18** *ROM of manzamine A **230***.[143]

a) i) HCl; ii) Grubbs I, ethylene, $CH_2Cl_2$, r.t., 24 h, 71%, **231**:**232** 4:1.

### 3.4.3 RRM in DOS

Towards the end of our investigation into the RRM of our substrates, an example of the application of RRM to a DOS library was reported (**Scheme 3.19**).[149] In this example the key step for the generation of molecular scaffold **233** required a RRM of highly strained norbornene derivative **234**. This generated 1,3-diene **235** that was then converted to scaffold **233** using a Diels-Alder reaction. Variation of the *N*-alkyl group and the dienophile would enable the incorporation of further diversity. RRM is therefore clearly a powerful tool in DOS library synthesis, and the generation of methodology to enable unstrained cycloalkenes to be used for this purpose would be of great value.

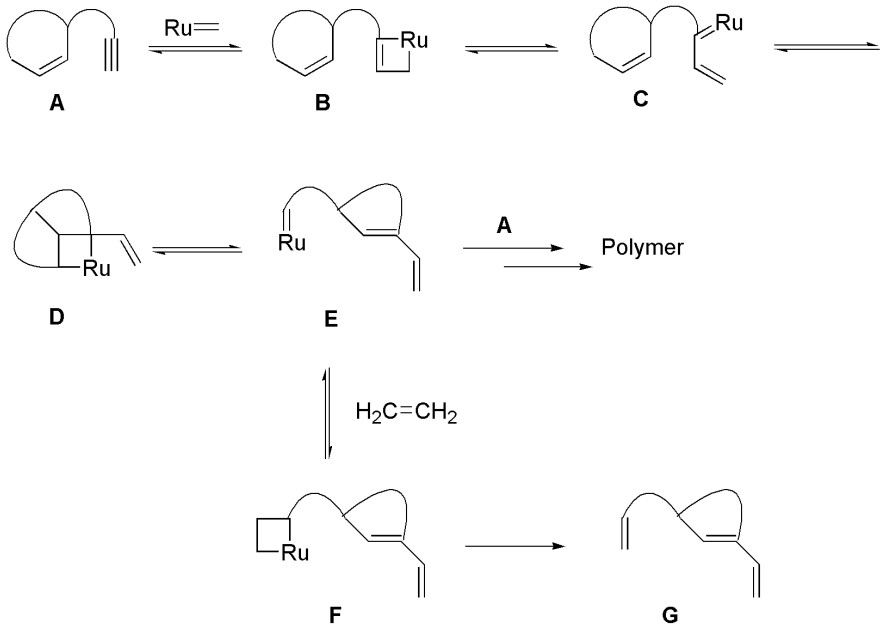



**Scheme 3.19** *Application of enyne metathesis in DOS library synthesis.*[149]

a) Grubbs I (10 mol%), ethylene, MW, 60 °C, 1 h; b) Grubbs I (10 mol%), Grubbs II (10 mol%), ethylene, MW, 60 °C, 2 h; c) CN-$CH_2CO_2K$, MeOH, 1 h, 87% (over 3 steps); d) *N*-ethylmaleimide, PhMe, MW, 160 °C, 6 h. 99%.

### 3.4.4 Mechanism

It is postulated for all RRM reactions involving pendant alkynes, that the ruthenium catalyst first reacts with the more electron rich alkyne part, rather than facilitating the cycloalkene ring-opening immediately. The proposed mechanism for the RRM of a cycloalkene-yne has been briefly discussed in the literature, and is represented in **Scheme 3.20** for the RRM of a substrate whose alkyne tether is connected to the C-3 position of the cycloalkene.[146]

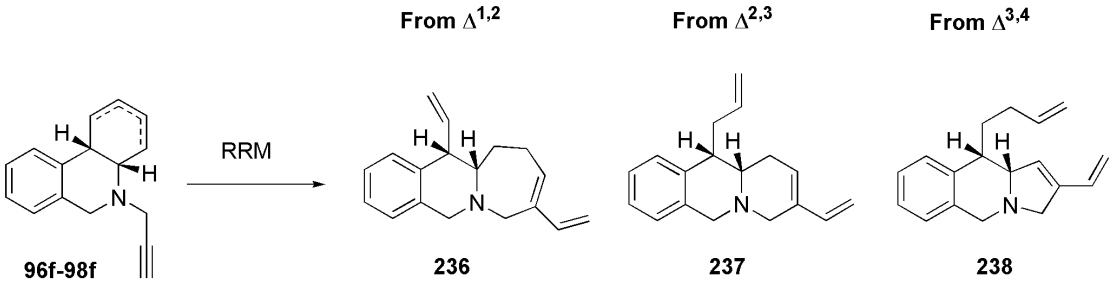



**Scheme 3.20** *Proposed mechanism for RRM.*[146]

The alkyne part of substrate **A** reacts with the ruthenium complex to generate ruthenocyclobutene **B**. This gives rise to ruthenium-carbene complex **C** by ring-opening through cycloreversion. The carbene complex can then react intramolecularly with the cycloalkene part to generate the highly-strained ruthenium complex **D**, which then undergoes ring-opening to afford carbene complex **E**. The ruthenium-carbene **E** is unable to undergo further intramolecular reaction at this stage and as a result it will react with another molecule of **A** to afford a polymer (e.g ROMP). However, if the reaction is carried out under an atmosphere of ethylene, ruthenium complex **E** would react with the gas to give RRM product **G** via ruthenacyclobutane **F**.

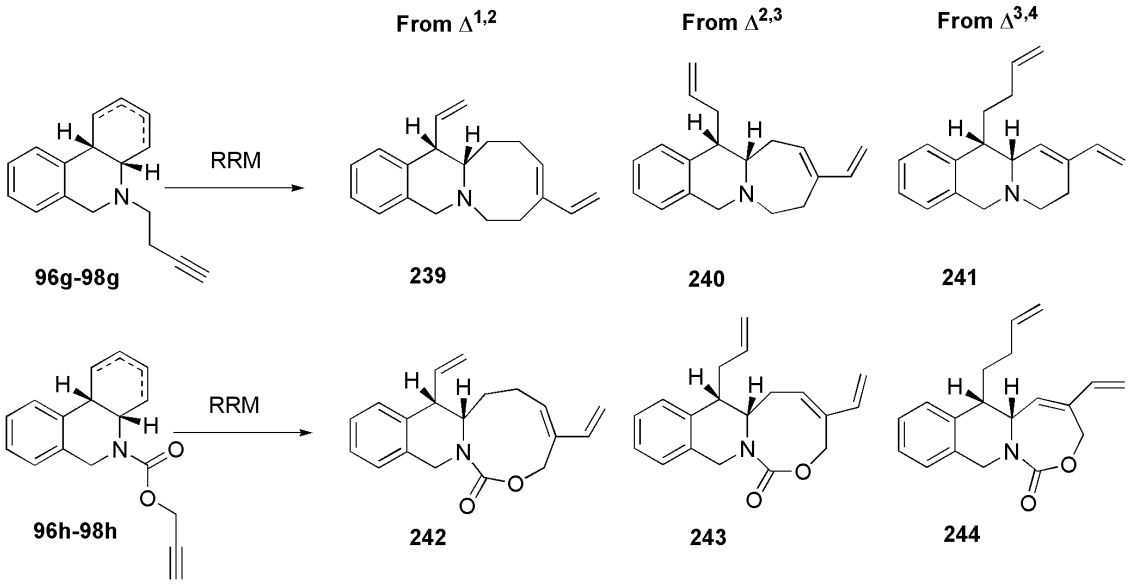
### 3.4.5 Proposed RRM of the phenanthridine core

We were aware from literature examples (**section 3.4.2**) that the RRM product varies depending on the size of the cycloalkene, the length of the alkyne tether, and the position of the alkene bond within the cycloalkene. We envisaged using this to our advantage in a RRM of our phenanthridine double bond isomer mixture. *N*-propargylation of our phenanthridine, followed by RRM would yield three skeletally different products using one common reaction (**Scheme 3.21**). In conjunction with aryl variation, a powerful and efficient approach to a DOS library may be realised.




**Scheme 3.21** *Potential products from the RRM of propargyl phenanthridines* ***96-98f.***

In addition to the propargyl group, we also proposed to investigate the homopropargyl and Poc-protected analogues **96gh**-**98gh** to potentially give us access to larger ring cycloalkene and cyclic carbamate products (**Scheme 3.22**).

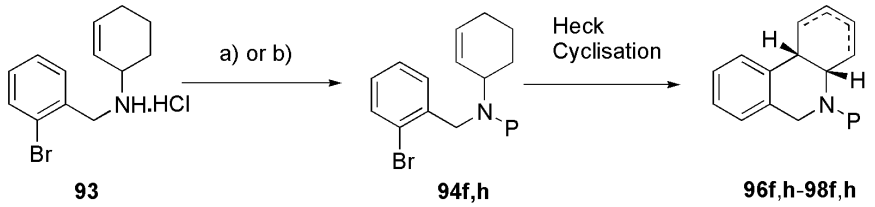



**Scheme 3.22** *Potential products from the RRM of homopropargyl and Poc phenanthridine derivatives* ***96-98g*** and ***96-98h***.

### 3.4.6 Synthesis of RRM precursors

#### 3.4.6.1 Heck cyclisation approach

In light of the generally poor yields reported in the literature, and to simplify analysis of the reaction, we decided to trial the RRM on single double bond isomers. We knew that our Heck cyclisation under cationic conditions gave predominantly the $\Delta^{1,2}$ double bond isomer and so we decided to generate cyclisation precursors with the appropriate *N*-functional groups. To this end we prepared propargyl[150] and Poc-protected[151] starting materials **94f** and **94h** (**Scheme 3.23**).




**Scheme 3.23** *Synthesis and attempted cyclisation of propargyl precursors.*

a) P = $CH_2C{\equiv}CH$: propargyl bromide, $K_2CO_3$, DMF, r.t., 16 h, 99%; b) P = $C(O)OCH_2C{\equiv}CH$: PocCl, $Et_3N$, $CH_2Cl_2$, 0 °C → r.t., 16 h, 99%.

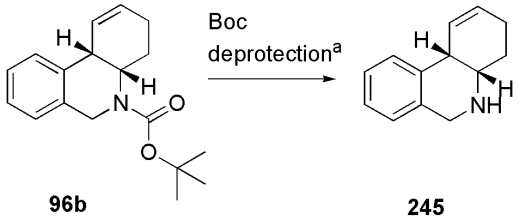
Cationic cyclisation of both substrates gave none of the desired product, and in the case of the Poc analogue **94h**, secondary amine **93** was recovered as the sole product. Application of our milder conditions using $(^tBu_3P)_2Pd$ at either r.t. or 50 °C gave similar results. Preparation and cyclisation of a homopropargyl analogue was not carried out due to these unsuccessful results.

#### 3.2.6.2 Attempted deprotection of *N*-Boc

As the Heck cyclisation of propargyl precursors **94f** and **94h** had failed, we realised that to access the required propargyl phenanthridines we needed to perform a Boc-deprotection of the appropriate phenanthridine, followed by protection with the relevant propargyl reagent. As the desired propargyl and homopropargyl products were amines we presumed that separation of the Boc-protected double bond isomers would be easier. To this end HPLC separation of **96b-98b** furnished us with sufficient quantities of the isolated double-bond isomers to take on to the next stage.

We had presumed that Boc-deprotection of **96b-98b** would be a trivial step, indeed we had easily removed the Boc-group from saturated analogue **110b** using TFA/$CH_2Cl_2$ when we proved the *cis*-ring junction stereochemistry of our phenanthridines (see **section 2.5.2**). However, in this case we had an alkene that was capable of unwanted isomerism under acid-catalysis conditions (see **section 2.9.4**), so we were forced to investigate alternative conditions by which to remove the Boc group from our phenanthridines **(Table 3.10)**.

**Table 3.10** *Conditions for the Boc-deprotection of* $\Delta^{1,2}$ *phenanthridine* ***96b***.




**96b** **245**

| Entry | Conditions[a] | T (°C) | t (h) | Conversion (%) | Notes $\Delta^{1,2}$: $\Delta^{2,3}$:$\Delta^{3,4}$ |
|---|---|---|---|---|---|
| 1 | TFA, $CH_2Cl_2$ | r.t. | 0.5 | 100 | 81:18:1 mixture of d.b. isomers |
| 2 | TFA, $CH_2Cl_2$ | 0 | 1 | 100 | 61:19:20 mixture of d.b. isomers |
| 3 | $ZnBr_2$ (2.7 eq), $CH_2Cl_2$ | r.t. | 16 | 100 | 77:0:23 mixture of d.b. isomers |
| 4 | CAN (0.2 eq), MeCN | 80 | 16 | 100 | Many products |
| 5 | CAN (2 eq), MeCN | 80 | 16 | 100 | Many products |
| 6 | $SnCl_4$ (4 eq), EtOAc | r.t. | 16 | n.d | S.M. + several products |
| 7 | TBAF (10 eq), THF | 80 | 16 | n.d | S.M. + several products |
| 8 | $Na_2CO_3$, DME/$H_2O$ | 80 | 72 | 0 | S.M. recovered |
| 9 | FVP | 500 | 0.5 | n.d | Posible product formation |
| 10 | FVP | 600 | 0.5 | 60 | $\Delta^{1,2}$ isomer only |

Entries **1** and **2** confirm that double bond isomerism occurred under standard TFA Boc-deprotection conditions, even at 0 °C. Lewis acid mediated deprotection using $ZnBr_2$[152] gave a mixture of double bond isomers (entry **3**) and incomplete deprotection/unidentifiable product formation using $SnCl_4$[153] (entry **6**). Ceric ammonium nitrate (CAN) has been reported as a successful one-electron transfer catalyst for the removal of the Boc-group from a range of amines, alcohols and thiols.[154] However in our case, although complete removal of the Boc-group was observed, a mixture of unidentifiable products was obtained, rendering this approach

ineffective for our purposes (entries **4** and **5**). TBAF has been shown to be an effective Boc-deprotecting agent for a range of aryl and heteroaryl substrates,[155] however application of these conditions to $\Delta^{1,2}$ phenanthridine **96b** led to incomplete conversion and a mixture of unidentifiable products. $Na_2CO_3$ in DME/$H_2O$ has been used for the *N*-Boc deprotection of various heteroaryl amines,[156] but no conversion was observed on our system. The conditions we finally used for selective deprotection of the Boc-group without double bond isomerism required flash vacuum pyrolysis at 600 °C (entry **10**).[157]

### 3.4.6.3 Flash vacuum pyrrolysis (FVP) deprotection of *N*-Boc

Flash vacuum pyrolysis refers to the gas-phase pyrolysis of an organic material under low-pressure conditions.[158,159] In its simplest form FVP involves vacuum distillation of an organic substrate through an empty hot pyrolysis tube, contained within a furnace (**Figure 3.10**). The products are simply collected afterwards in a U-tube contained within a cold trap, and generally require no work up and little purification.

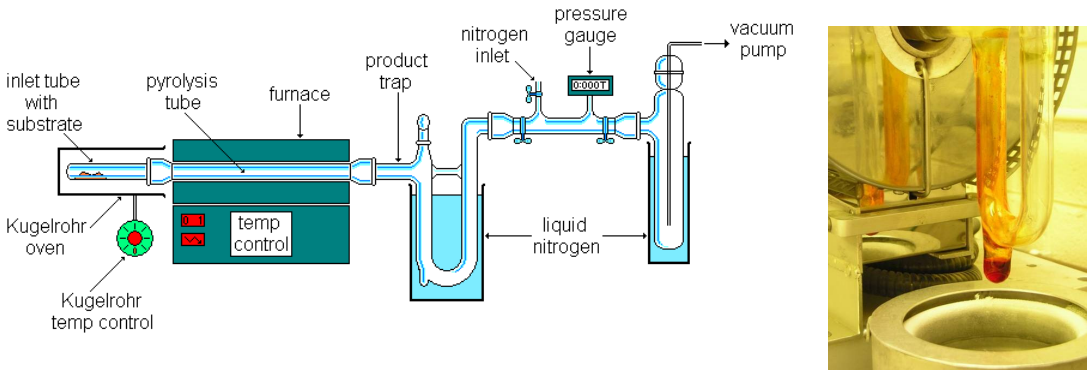
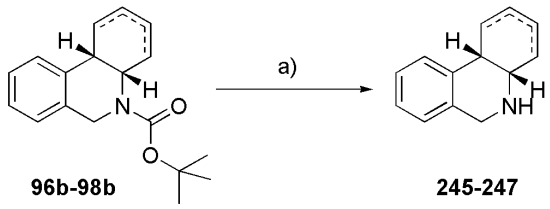



**Figure 3.10** *Diagram of the FVP apparatus and a photograph of a typical FVP product collecting in the U-tube.*[158]

FVP has significant advantages over condensed-phase methods because there are no solvent or reagent molecules present to interfere with the reactive intermediate. In addition to this, the ultra-high vacuum employed for FVP means that the molecules undergoing reaction spend mere milliseconds in the reaction zone (i.e the pyrolysis tube) before they are quenched. This means that even thermally unstable reactive intermediates usually survive FVP conditions.[158,159]

The use of FVP to facilitate Boc-deprotection has been reported,[157,160] and typically requires a furnace temperature of 600 °C. As reported in **Table 3.10** we found that successful Boc-deprotection under these conditions was achieved for $\Delta^{1,2}$ phenanthridine **96b**, and we were pleased to discover that this also held true for the $\Delta^{2,3}$ and $\Delta^{3,4}$ phenanthridines **97b** and **98b** (**Scheme 3.24**). Purification of the reaction products was achieved through subsequent Kugelrohr distillation.



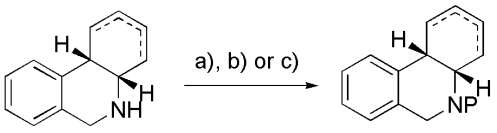

**Scheme 3.24** *FVP mediated Boc-deprotection of isolated phenanthridines **96b-98b**.*
a) i) FVP, 600 °C, 0.5 h; ii) Kugelrohr distillation 70 °C, $\Delta^{1,2}$ **245** 60%, $\Delta^{2,3}$ **246** 81%, $\Delta^{3,4}$ **247** 71%.

### 3.4.6.4 RRM precursors via alkylation/acylation

With each of the three double-bond isomer amines **245-247** in hand, we set about synthesising the corresponding propargyl, homopropargyl and Poc-protected analogues. Unfortunately, the conditions we had used previously for the propargylation of secondary amine **93** (propargyl bromide, $K_2CO_3$, DMF, **Scheme 3.23**)[150] did not prove to be successful on the phenanthridine substrates **245-247**, furnishing the desired products in <10% yield. Our group had experience of *N*-propargylations, and it was suggested that the formation of side products was occurring due to the lengthy reaction time employed. The use of dry acetone and an elevated reaction temperature was suggested in order to increase the solubility of the $K_2CO_3$ and thus accelerate the reaction. After 2 h all three propargylated products **96f-98f** were recovered in good yield (**Table 3.11**). Similar conditions were employed to access homopropargyl phenanthridines **96g-98g**, although these reactions required heating for 16 h to achieve reasonable conversions. Finally, Poc-protected phenanthridines **96h-98h** were obtained following reaction of a mixture of **245-247** with propargyl chloroformate as previously. Purification of mixture **96h-98h** was easier as the substrates were carbamates and not amines and therefore less

polar. This enabled us to obtain sufficient isolated quantities of Poc-phenanthridines **96h-98h** to use in our RRM studies.

**Table 3.11** *RRM precursor synthesis.*




**245-247**

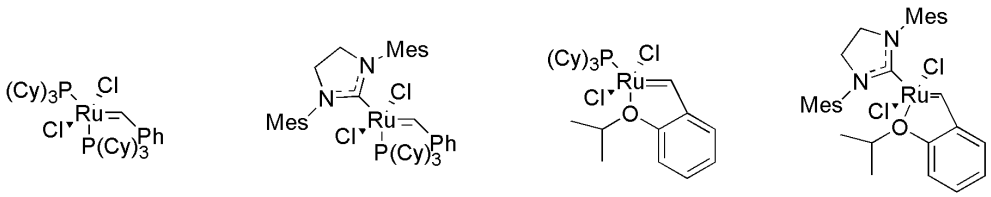
P= propargyl: **96f-98f**
P=homopropargyl: **96g-98g**
P=Poc: **96h-98h**

| Entry | Substrate | Conditions | T ($^{o}$C) | t (h) | Product | Conversion (%) |
|---|---|---|---|---|---|---|
| 1 | **245** | a | 60 | 2 | **96f** | 57 |
| 2 | **246** | a | 60 | 2 | **97f** | 75 |
| 3 | **247** | a | 60 | 2 | **98f** | 91 |
| 4 | **245** | b | 60 | 16 | **96g** | 55 |
| 5 | **246** | b | 60 | 16 | **97g** | 63 |
| 6 | **247** | b | 60 | 16 | **98g** | 73 |
| 7 | **245-247**[a] | c | 0 $^{o}$C→r.t. | 16 | **96h-98h**[a] | 74 |

a) P=$CH_2C{\equiv}CH$: propargyl bromide (1.1 eq), $K_2CO_3$ (3 eq), acetone (dry); b) P=$CH_2CH_2C{\equiv}CH$: homopropargyl bromide (1.1 eq), $K_2CO_3$ (3 eq), acetone (dry); c) P=$C(O)OCH_2C{\equiv}CH$: PocCl (4 eq), $Et_3N$ (4 eq), $CH_2Cl_2$, 0 $^{o}$C → r.t. [a] Mixture.

### 3.4.7 RRM studies – Propargyl analogues

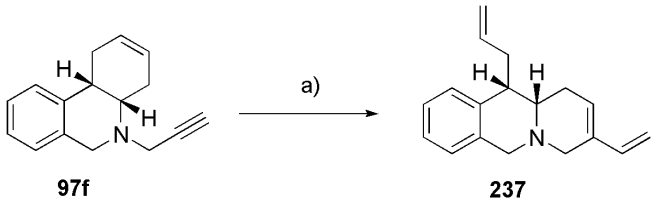
The majority of recent Grubbs metathesis literature focuses on the use of four main catalysts: Grubbs I **248**; Grubbs II **249**; Hoveyda-Grubbs I **250**; and Hoveyda-Grubbs II **251** (**Figure 3.11**). We initially decided to employ Hoveyda-Grubbs II **251** as our Ru source as this was the most recent generation catalyst and had precedent in ROM-polymerisation reactions.[161]




**248** **249** **250** **251**

**Figure 3.11** *Commercially available Grubbs-metathesis catalysts.*

We were delighted to observe that application of catalyst **251** to $\Delta^{2,3}$ propargyl phenanthridine **97f** under an atmosphere of ethylene, led to formation of benzo[*b*]quinolizine product **237** in excellent yield (**Scheme 3.25**). We had presumed that this particular propargyl substrate would be most likely to undergo a successful RRM as it gave rise to a conformationally favoured 6,6,6-ring annulated product.

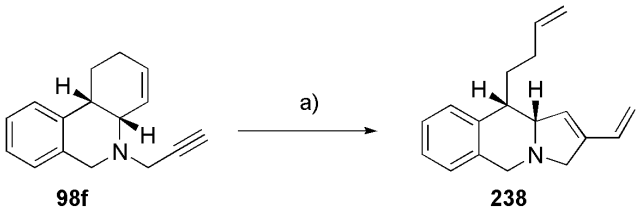



**97f** **237**

**Scheme 3.25** *RRM of $\Delta^{2,3}$ propargyl phenanthridine **97f**.*

a) Hoveyda-Grubbs II **251** (15 mol%), ethylene, $CH_2Cl_2$, r.t., 40 h, 71%.

Following the success of this result, we applied these conditions to other propargyl phenanthridines **96f** and **98f**. Disappointingly, we observed quantitative recovery of the starting material upon the attempted RRM of $\Delta^{1,2}$ propargyl-phenanthridine **96f**. Presumably in this instance, the alkene was too far away for the propargyl tether to access it for the metathesis reaction. Performing this reaction at elevated temperature had no impact on the result. However, we were pleased to discover that $\Delta^{3,4}$ propargyl-phenanthridine **98f** gave total conversion to the benzoindolizine product **238** (**Scheme 3.26**).




**98f** **238**

**Scheme 3.26** *RRM of $\Delta^{3,4}$ propargyl phenanthridine **98f**.*

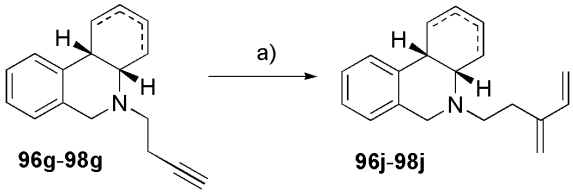
a) Hoveyda-Grubbs II **251** (15 mol%), ethylene, $CH_2Cl_2$, r.t., 40 h, 80%.

### 3.4.8 RRM of homopropargyl analogues

The RRM of both $\Delta^{2,3}$ and $\Delta^{3,4}$ propargyl phenanthridines **97f** and **98f** were remarkable results given the lack of similar unstrained cycloalkene examples in the literature. However, in order for the reaction to be of use to us in a DOS library context, we required an RRM that was applicable to all three double bond isomers. We were hopeful that extension of the alkynyl chain by one or two atoms, would allow it to be long enough to undergo metathesis with the $\Delta^{1,2}$ alkene.

To this end, homopropargyl-phenanthridines **96g-98g** were subjected to our RRM conditions (**Table 3.12**). Total conversion was observed in all cases, and the product exhibited the same mass and the correct number of $^{1}H$ and $^{13}C$ signals in the NMR as the desired RRM products **239-241**. In addition to this, we observed the alkene quartet signal at 6.40 ppm that had been very distinctive in the $^{1}H$ NMR spectrum of **237** and **238**.

**Table 3.12** *Attempted RRM of isolated homopropargyl-phenanthridines* ***96g-98g***.




| Entry | Substrate | Catalyst | Product | Conversion (%) |
|---|---|---|---|---|
| 1 | **$\Delta^{1,2}$** | **251** | **96j** | 69 |
| 2 | **$\Delta^{2,3}$** | **251** | **97j** | 54 |
| 3 | **$\Delta^{3,4}$** | **251** | **98j** | 67 |
| 4 | **$\Delta^{2,3}$** | **248** | **97j** | 99 |
| 5 | **$\Delta^{2,3}$** | **248** | **97j** | 89[a] |

a) Hoveyda-Grubbs II **251** or Grubbs I **248** (15 mol%), ethylene, $CH_2Cl_2$, r.t., 40 h [a] at 45 °C.

However, in one of the literature examples illustrated (**Table 3.8**),[146] two potential products from the treatment of an cycloalkene-yne with ethylene in the presence of a metathesis catalyst are identified. In addition to the desired RRM product (such as benzo[*b*]quinolizine **237** and benzoindolizine **238**), the formation of a 1,3-diene can

occur from the metathesis of the alkyne with ethylene, without concommitant RRM. This would afford a product with the same mass, number of protons and number of carbons as the desired RRM product, leading to easy misinterpretation. We eventually assigned products **96j**-**98j** as the undesired 1,3-dienes by careful analysis of the splitting pattern in the alkene region of the $^{1}$H NMR spectra.

For benzo[*b*]quinolizine RRM product **237** (**Figure 3.12**), each of the four terminal alkene signals (a+h) appear as doublets as a result of the proton (b or g) on the adjacent carbon. For the 1,3-diene product **97j** (**Figure 3.13**), two of the terminal alkene signals appear as doublets (k1+k2) as a result of the proton (j) on the adjacent carbon, and the two remaining terminal alkenes appear as broad singlets (indicative of h). Proton b of the RRM product **237** is a high order multiplet, strongly indicative of its position adjacent to a and c. In addition to this, protons b and c of 1,3-diene **97j** are positioned where we normally find the $\Delta^{2,3}$ isomer alkene signals of the phenanthridine. The two NMR examples given are typical of the other RRM and 1,3-diene products and further structural confirmation was obtained from 2D COSY NMR studies.

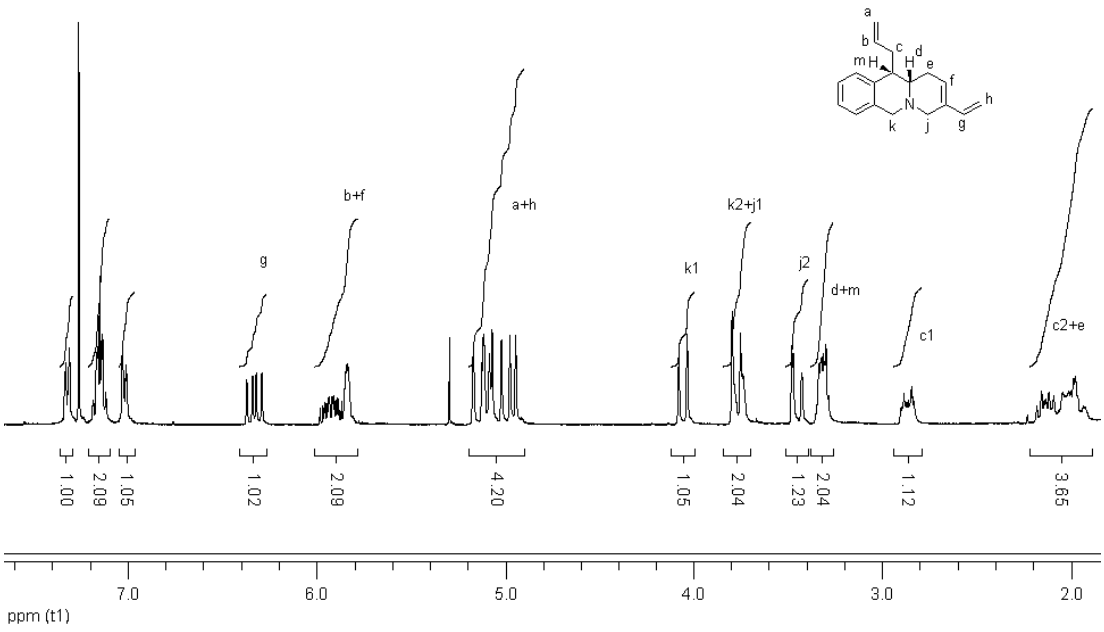



**Figure 3.12** *$^{1}$H NMR of benzo[b]quinolizine RRM product **237**.*

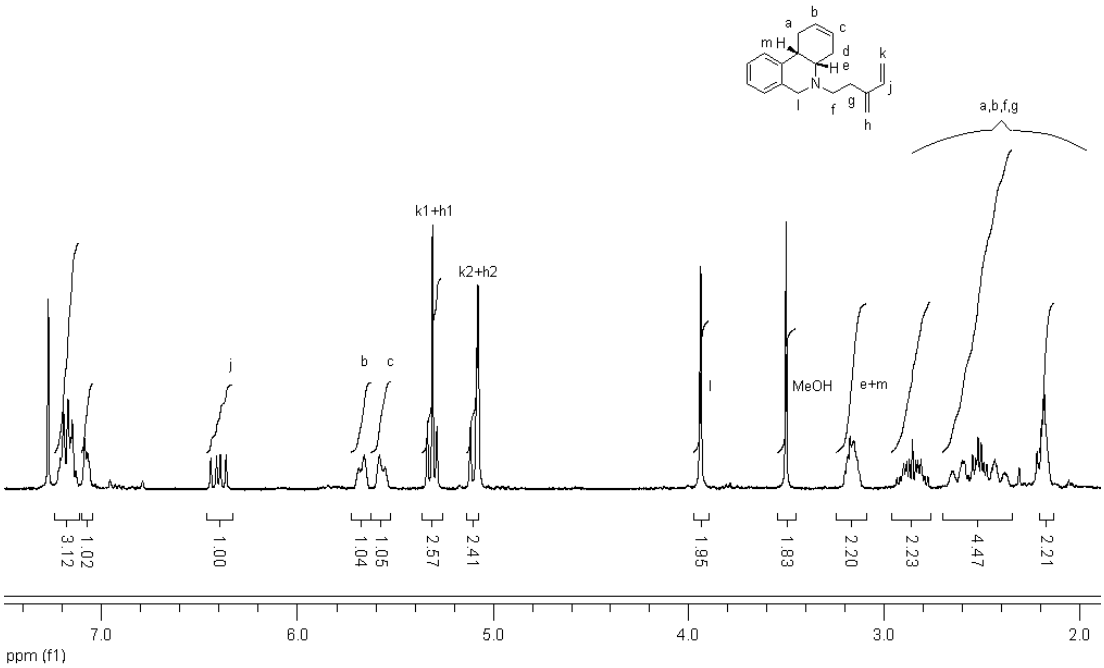
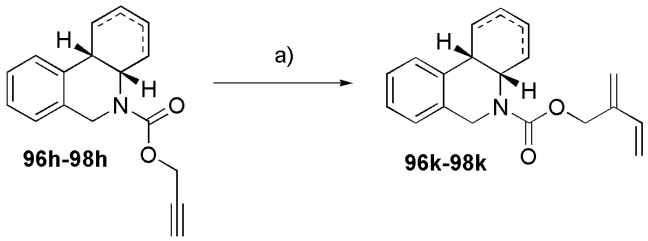



**Figure 3.13** *$^{1}H$ NMR of $\Delta^{2,3}$ diene* ***97j.***

### 3.4.9 Other metathesis attempts

Similarly, the application of our standard metathesis conditions to Poc-phenanthridines **96h-98h** also gave the corresponding 1,3-diene products **96k-98k** (**Table 3.13**). Despite substrates **96h-98h** failing to undergo RRM, we were pleased to observe that the carbamate functionality of the Poc-group had remained in tact. As far as we know, this is the first report of such functionality surviving Grubbs-metathesis conditions, providing evidence to support its application in RCM studies.

**Table 3.13** *Attempted RRM of isolated Poc-phenanthridines* ***96h-98h.***

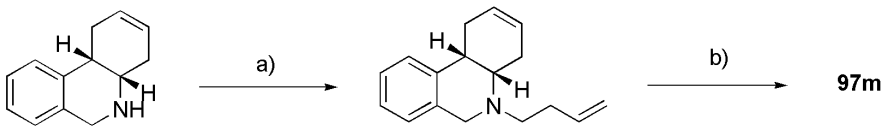



| Entry | Substrate | Product | Conversion (%) |
|---|---|---|---|
| 1 | **$\Delta^{1,2}$** | **96k** | 73 |
| 2 | **$\Delta^{2,3}$** | **97k** | 60 |
| 3 | **$\Delta^{3,4}$** | **98k** | 96 |

a) Hoveyda-Grubbs II **251** (15 mol%), ethylene, $CH_2Cl_2$, r.t., 40 h.

As suggested in **section 3.4.2**, the formation of 1,3-diene products has been proposed to occur as a result of steric congestion.[146] In light of this, we were keen to observe what happened when we employed the less sterically hindered Grubbs I catalyst **248**, which had found success in the literature precedent. However, application of this catalyst to the $\Delta^{2,3}$ homopropargyl substrate **97g** at room temperature or 45 $^{o}$C in $CH_2Cl_2$ (**Table 3.12**), gave quantitative conversion to the 1,3-diene product **97j**, as we had previously observed using Hoveyda-Grubbs II **251**.

One additional literature example reported the successful manipulation of a butenyl tether in the RRM of indolizidine alkaloids.[162] As the homopropargyl and Poc-tethered phenanthridines had both formed the 1,3-diene under RRM conditions, we decided to synthesise butenyl-phenanthridine **97m**. If this substrate were to undergo an alkene cross metathesis with ethylene, it would simply regenerate the starting material, thus we were hopeful that an RRM would be promoted under such circumstances. However, unfortunately when we attempted this reaction on the $\Delta^{2,3}$ substrate **97m** using catalyst **251**, all we recovered was the starting material in quantitative yield, suggesting that either a cross alkene metathesis with ethylene had occurred, or that the alkene tether was unreactive.




**246** **97m**

**Scheme 3.27** *Synthesis and attempted RRM of $\Delta^{2,3}$ butenyl-phenanthridine* ***97m***. a) Butenyl bromide (1.1 eq), $K_2CO_3$ (3 eq), acetone (anhydrous); b) **251** (15 mol%), ethylene, $CH_2Cl_2$, r.t., 40 h, 99%.

### 3.4.10 Conclusions for RRM

Several interesting points were raised from these preliminary investigations into the RRM of our phenanthridine substrates. Firstly, the reaction was clearly possible as exemplified by the successful synthesis of benzo[*b*]quinolizine **237** and benzoindolizine **238**. As we have seen from the molecular model of a typical *cis*-phenanthridine (**Figure 3.6**), the molecule lies in a very cupped conformation as

compared to its flatter *trans* counterpart. Our working hypothesis as to the success of these RRM reactions, is that the relief of steric strain upon opening of the C-ring provides a strong driving force for the reaction. In order to test this hypothesis it would certainly be interesting to try the same RRM reaction on an analogous *trans*-phenanthridine. The formation of the conjugated diene in the RRM product, may also contribute to promotion of the RRM reaction.

The second interesting point is the formation of 1,3-dienes from the longer alkyne-tethered phenanthridines, rather than the desired RRM product. There are currently no reports in the literature comparing the relative abilities of propargyl and homopropargyl tethers to undergo RRM. However, instances of both being successfully manipulated in RRM are known, as are instances of both acting as precursors for formation of the 1,3-diene product.[146] As we obtained no improvement using a less bulky catalyst (Grubbs I **248**) we can only postulate that the reluctance of our long-chain alkynyl tethered phenanthridines to undergo RRM may be a result of the disfavoured formation of larger C-ring products. This may also have some bearing on the failed RRM of the propargyl $\Delta^{1,2}$ analogue as the product here would have had a 7-membered C-ring, however it is likely in this case that the tether was simply to short to allow the RRM reaction to take place.

In light of the time constraints for this project we had to be content with limiting our skeletal diversification to the successful generation of two RRM products. However, the work sets excellent precedent for further investigation into *cis* vs *trans* ring-fused cyclohexenes as substrates for RRM reactions.

### 3.5 Conclusions

Methodology for the synthesis of a DOS library of phenanthridines was explored from each of the three possible angles, namely building block diversity, stereochemical diversity and skeletal diversity.

*i) Building block diversity*

Conditions for the high yielding and efficient synthesis of various aromatic/heteroaromatic building blocks were developed, using standard transformations, or less standard Curtius methodology. These building blocks were readily converted to the corresponding cyclisation precursors **165a-f,k**, and shown to undergo facile Heck cyclisation under cationic or neutral conditions, to afford the expected double bond isomer products **195**-**197a**-**f**,**k** in excellent yield (72-99%).

*ii) Stereochemical diversity*

The synthesis of *exo*-syn dihydroxylated phenanthridines **206m**-**208m** was shown to proceed with high dr (>83:17) and excellent yield (99%) across the range of double bond isomers. Attempts to introduce epoxide functionality to the C-ring were hampered by over-oxidation to the phenanthridone or failure to reproduce reported literature conditions. We were therefore unable to generate any *trans*-diol C-ring phenanthridines.

*iii) Skeletal diversity*

Methodology for the RRM of various propargyl-tethered phenanthridines was explored. High conversions were obtained for the RRM of $\Delta^{2,3}$ and $\Delta^{3,4}$ propargyl phenanthridines **97f** and **98f** giving a potential route to novel benzo[*b*]quinolizines and benzoindolizine products. Unfortunately the propargyl tether did not react with the $\Delta^{1,2}$ alkene, preventing this methodology from being applied to all members of the alkene library, and thus limiting its use in a DOS library context. Our attempts to lengthen the alkynyl tether led to the formation of unwanted 1,3-diene products **96jk**-**98jk**.

Exploration of the amine building block diversity in conjunction with the *cis*-dihydroxylation protocol will be the two elements combined in **Chapter 4** for the DOS library synthesis.

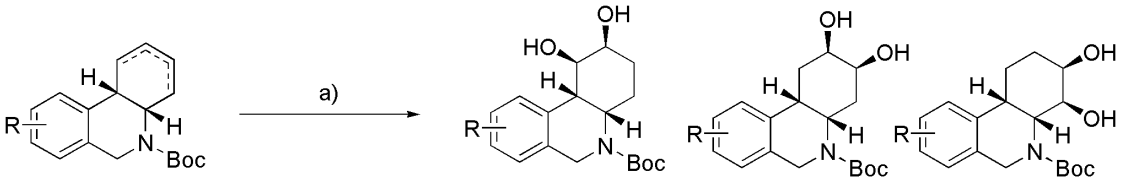
# *RESULTS AND DISCUSSION PART 3*
# CHAPTER 4

## LIBRARY SYNTHESIS AND BIOLOGICAL EVALUATION

### 4.1 Library synthesis

We chose to synthesise a library based upon the phenanthridine core, using the building block and stereochemical diversity protocols developed in **Chapter 3**. To this end our aryl and heteroaryl double bond isomer phenanthridine mixtures **195-197a-f**,**k** were treated under *exo cis*-dihydroxylation conditions (**Table 4.1**) to afford the corresponding diol mixtures **206**-**208a-f**,**k**.

**Table 4.1** *Cis-dihydroxylation of aryl/heteroaryl phenanthridines **195-197a-f,k**.*




**195-197a-f,k** **206a-f,k** **207a-f,k** **208a-f,k**

| Entry | 195-197 | Substrate (R= ) | Yield 206-208 (%)[a] | Yield 206 (%)[b] | Yield 207 (%)[b] | Yield 208 (%)[b] |
|---|---|---|---|---|---|---|
| 1 | a | 4-Me | 78 | - | - | - |
| 2 | b | 4-F | 82 | 18 | 28 | 20 |
| 3 | c | 5-MeO | 95 | 13 | 12 | 19 |
| 4 | d | 4,5-diMeO | 70 | 6 | 19[c] | 30 |
| 5 | e | [*Naphthyl*][$] | 87 | 14 | 28 | 16 |
| 6 | f | [*Thiophene*][$] | 64 | - | - | - |
| 7 | k | [*Piperonyl*][$*] | 87 | 9 | 23 (2)[d] | 18 |
| 8 | m (**96b-98b**)[e] | H | 70 | 13 | 11 | 12 |

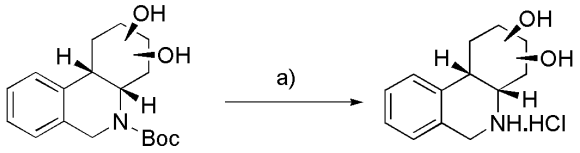
a) $OsO_4$, NMO, THF/$H_2O$, r.t., 18 h. [a] Isolated yield for mixture following flash chromatography. [b] Isolated yield of each isomer following flash chromatography or additional HPLC separation. [c] comprises approximately 1:1 mixture of $\Delta^{1,2}$:$\Delta^{2,3}$ diols. [d] $\Delta^{2,3}$ *endo-syn* diol product **209k** isolated and characterised by 2D NMR studies (see **section 3.3.2**). [e] Reaction performed on parent phenanthridines **96b**-**98b**. [$] See footnote **Table 3.2**. * As in **Scheme 3.6**.

In keeping with the high diasteromeric ratio we obtained for the *cis*-dihydroxylation of carbamates **96b-98b** in the previous chapter (**Table 3.7**), we observed the *exo*-diols as the major products. Determination of the exact ratio was not possible due to the complex mixture of isomer products. Structural assignment was made by analogy with the parent diol analogues **206m**-**208m** (R=H) that were synthesised as isolated products in the previous section (**Table 3.7**). The dihydroxylation of **96b**-**98b** was repeated here using the mixture of double bond isomers to give a comparative result for the library synthesis (**Table 4.1**, entry **8**). From the dihydroxylation of piperonyl phenanthridines **195k-197k** (entry **7**) we isolated a trace amount of the $\Delta^{2,3}$ *endo-syn* diol **209k** that enabled us to confirm the major and minor product structures using 2D nOESY NMR (see **section 3.3.2**).

Following dihydroxylation, the three major products **206**, **207** and **208** were isolated by silica-gel chromatography or HPLC separation, and in the majority of cases reasonable amounts of each were recovered (**Table 4.1**). However, unfortunately we were not able to separate the 4-methyl diol products **206a-208a** despite repeated attempts. Similarly, the $\Delta^{1,2}$ and $\Delta^{2,3}$ dimethoxy analogue fractions **206d** and **207d** overlapped significantly in the HPLC separation and thus the $\Delta^{2,3}$ sample had significant $\Delta^{1,2}$ contamination. Additionally, due to the unselective Heck cyclisation of thiophene analogue **165f**, we did not think it feasible to carry out HPLC separation of its diol counterparts. For these three substrates, mixtures of the appropriate compounds **206**-**208a**,**f**,**k** were carried through to the biological testing stage.

For the last step in our library synthesis, we took the diol mixtures (with the exception of **206-208e,m**) and isolated compounds and converted each into the hydrochloride salts, with yields as summarised in **Table 4.2**. In general, and where available, the diol mixtures were used in preliminary biological investigations, so that precious isolated material was not wasted.

**Table 4.2** *Boc deprotection to afford a phenanthridinium hydrochloride library.*

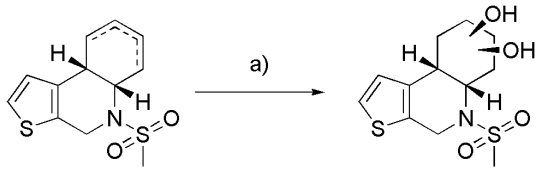



**206-208a-f,k,m** **252-254a-f,k,m**

| Entry | 206-208 | Substrate (R=) | Yield 252-254 (%)[a] | Yield 252 (%) | Yield 253 (%) | Yield 254 (%) |
|---|---|---|---|---|---|---|
| 1 | a | 4-Me | 69 | - | - | - |
| 2 | b | 4-F | 99 | 99 | 86 | 74 |
| 3 | c | 5-MeO | 89 | 82 | 92 | 84 |
| 4 | d | 4,5-diMeO | 87 | 88 | 60[b] | 60 |
| 5 | e | [*Naphthyl*][$*c] | - | 67 | 61 | 69 |
| 6 | f | [*Thiophene*][$*] | 99 | - | - | - |
| 7 | k | [*Piperonyl*][$*] | 69 | 61 | 81 (60)[d] | 77 |
| 8 | m | H[c] | - | 86 | 60 | 53 |

a) i) TFA, $CH_2Cl_2$, 1 h, r.t.; ii) NaOH, adjust to pH 9; iii) HCl in $Et_2O$, 0 °C. [a] Performed on mixture. [b] Approximately 1:1 mixture $\Delta^{1,2}$:$\Delta^{2,3}$. [c] As reasonable quantities of the isolated isomers were available, no mixture of hydrochloride salts was synthesised for these analogues. [d] Yield for deprotection of *endo-syn* piperonyl substrate **209k** to afford diol hydrochloride **255k**. [$] See footnote **Table 3.2**. * As in **Scheme 3.6**.

We also treated the sulfonamide protected thiophene mixture **158-160** to the *cis*-dihydroxylation conditions (**Scheme 4.1**). Purification by flash chromatography afforded isolated quantities of the three major *exo-syn* products, providing three additional compounds **256-258** for our library.




**158-160** **256-258**

**Scheme 4.1** *Cis-dihydroxylation of thiophene sulfonamides **158-160**.*

a) $OsO_4$, NMO, THF/$H_2O$, r.t., 18 h, 73%. Isolated yields: $\Delta^{1,2}$ **256**, 6%; $\Delta^{2,3}$ **257**, 6%; $\Delta^{3,4}$ **258**,14%; mixture, 47%.

The structures of the 22 isolated compounds and 6 mixtures that were synthesised for biological testing are shown in full below (**Figure 4.1**).

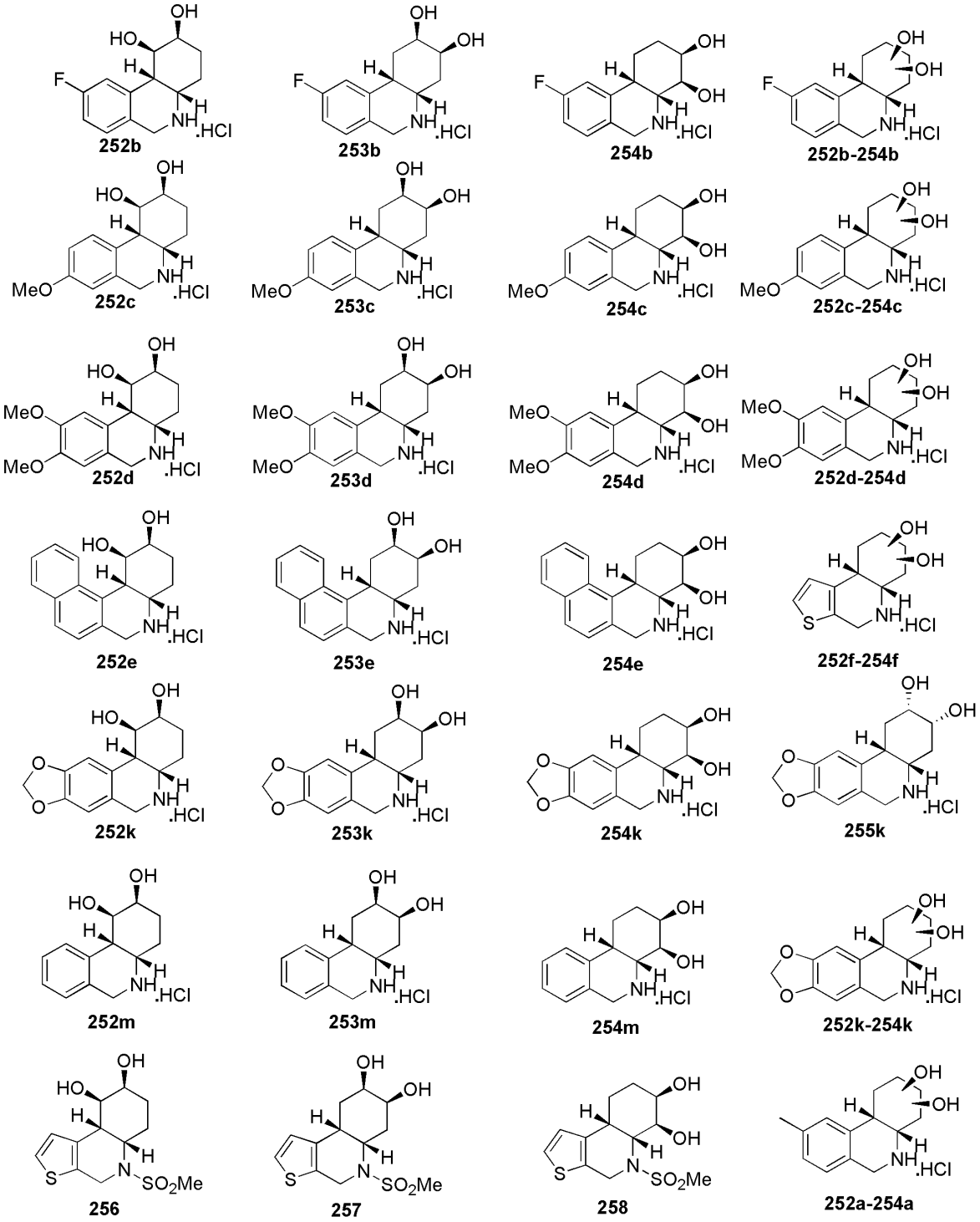



**Figure 4.1** *Phenanthridine diol library members for biological testing.*

### 4.2 Screening of small molecule libraries

As alluded to in **Chapter 1**, forward-chemical genetics describes a method of identifying small molecules that modulate the function of a biological pathway, resulting in an induction or reversion of a specific phenotype.[2] The use of whole organisms to facilitate phenotypic screening of compound libraries, is an area that has received significant attention recently.[163] In whole organisms the cells are not transformed, and are in their normal physiological environment offering significant advantages over traditional cell-based assays. Additionally, because the embryo contains many distinct cell-types, the identification of tissue-specific small molecules can be made. The use of whole organisms can also enable the screening of processes that are not easily replicated *in vitro* such as organ development. Finally, the metabolism of the organism permits the identification of compounds that become active as metabolites, something that is not possible in cell-based assays.

Carrying out *in vivo* screening right from the outset of a project can therefore save valuable time by providing a more accurate model in terms of toxicity, tissue-specificity and bioavailability.[163] The validation of drug targets has traditionally been performed in mammalian models such as the mouse, however high-throughput validation of compound libraries requires smaller organisms that can be easily produced, studied and stored in great numbers. In light of this, interest has turned towards lower phylogenetic organisms such as *Drosophila melanogaster* (fruit fly), *Caenohabditis elegans* (nematode worm) and *Danio rerio* (zebrafish).

### 4.3 Zebrafish

The zebrafish has been a popular pet for many years, but its use for research has increased dramatically over the last 15 years following the demonstration of its amenability to chemical genetics screens (**Figure 4.2**).

**Figure 4.2** *Adult zebrafish - male (bottom) and female (top).*

There are many reasons for the suitability of zebrafish to high-throughput phenotyping. For example, following mating, the female adult zebrafish can produce up to 300 eggs.[50] The breeding process is also very rapid, and a mating pair need only be set up the evening before the eggs are required. With multiple breeding pairs, sufficient eggs for the screening of large compound collections can be rapidly raised. Fertilisation occurs externally to the female's body meaning that each stage of embryonic development can be easily examined, and importantly, the zebrafish embryo is transparent for the first five days of development, making it suitable for a wide range of optical analysis. This also means that the identification of phenotypes can be easily made without the need to kill or dissect the organism. As each embryo measures less than 1 mm in diameter they can be easily studied in microwell plates, and because the zebrafish is an aquatic organism, compounds can be directly aliquoted into the embryo medium.

One of the most valid reasons for high-throughput screening in zebrafish is their close evolutionary relationship to humans. There is a strong homology between the genes of mammalians and zebrafish, and phenotypes have been identified that closely resemble human diseases.[164] In the past few years, several additional tools have been developed that greatly aid the use of the zebrafish as a model organism. For example, the zebrafish genome has now been fully sequenced, resulting in the availability of multiple DNA microarrays for expression-profiling experiments.[165]

Antisense morpholino oligonucleotides can be utilised to knock-down proteins, permitting validation in circumstances where the small molecule in question may have multiple targets.[166,167] Furthermore, transgenic lines[168] (**Figure 4.3**) and targeted mutations[169] can also be introduced, enabling forward-chemical genetics to be performed, where compounds are screened to observe a reversion of phenotype. Of additional interest is the ability of the zebrafish to regenerate fins, skin, the heart, and the brain in larval stages.[164]

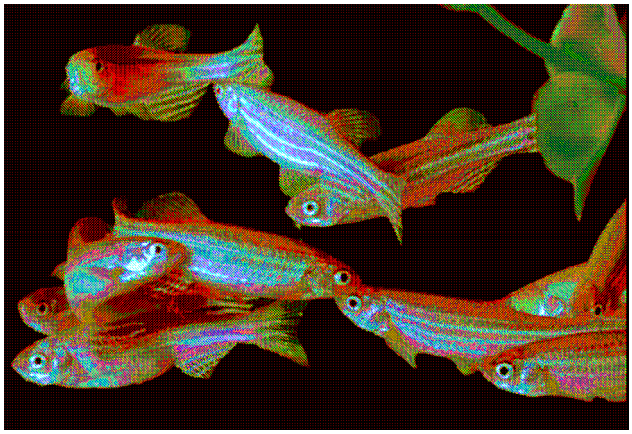


**Figure 4.3** *A colourful example of transgenic zebrafish, genetically modified with sea anemone genes.*[170]

Despite the numerous advantages of performing high-throughput phenotypic screening in zebrafish, there are several drawbacks. For true high-throughput screening, the number of compounds is limited to a few thousand per week due to the number of embryos obtainable. The amount of labour involved is greater than that of cell-based assays due to fish husbandry and lower overall throughput. Additionally, certain compounds that have proven to be potent in cell lines showed no activity in zebrafish.[171] The use of zebrafish assays should therefore be used as a complementary strategy to cell-based techniques, or as a secondary screening platform following a higher throughput primary screen.[172]

### 4.3.1 Practicalities of high-throughput phenotyping in zebrafish

In order to set up a small molecule zebrafish screen, a pair of adult zebrafish must first be mated to allow the embryos to be collected (**Figure 4.4**, **a**).[172] This is achieved by placing one male and one female in a small covered tank overnight, under darkness. When the lights are switched on the next morning the fish will mate and the embryos can be collected. Several clutches of embryos from different breeding pairs should be combined to minimise any unintended family effects from certain parents, or incorrectly genotyped fish. The embryos are washed with and stored in E3 medium that sustains their development.[ϕ] The embryos should be examined at this stage and any unfertilised eggs or dead embryos should be removed. Additionally, if dead embryos are noticed at any point during the screening process, they should be removed as they can be detrimental to the development and health of all the fish contained in their medium.

The embryos are incubated at 28.5 $^{o}$C until they reach the appropriate age of development, this is usually between 4 and 24 hours post fertilisation (hpf). Typically, two to three embryos are transferred to each well of a 96-well plate using a wide-tipped plastic Pasteur pipette (**Figure 4.4**, **b**).[172] The E3 medium is then decanted from the embryos using a Pasteur pipette and the appropriate small molecule is added at the relevant concentration in E3 (**Figure 4.4**, **c**&**d**). Drug concentrations tend to be in the range 1-100 μM for a preliminary screen, and it is standard to use up to 1% $^{v}/_{v}$ DMSO as a vehicle for transporting the small molecule across the cell membrane. Control experiments in E3 (plus up to 1% $^{v}/_{v}$ DMSO) are also performed so that the identification of phenotypes can be easily performed.

The development of the zebrafish embryos can then be carefully monitored over a period of five days, recording any phenotypes that arise (**Figure 4.4**, **e**). Any hits can then be traced back to the appropriate library member (**Figure 4.4**, **f**) and further assays carried out as appropriate.

[ϕ] E3 medium is comprised: 5 mM NaCl, 0.17 mM KCl, 0.4 mM $CaCl_2$, and 0.16 mM $MgSO_4$. To suppress the growth of mould the medium is supplemented with $10^{-5}$% methylene blue.[173]

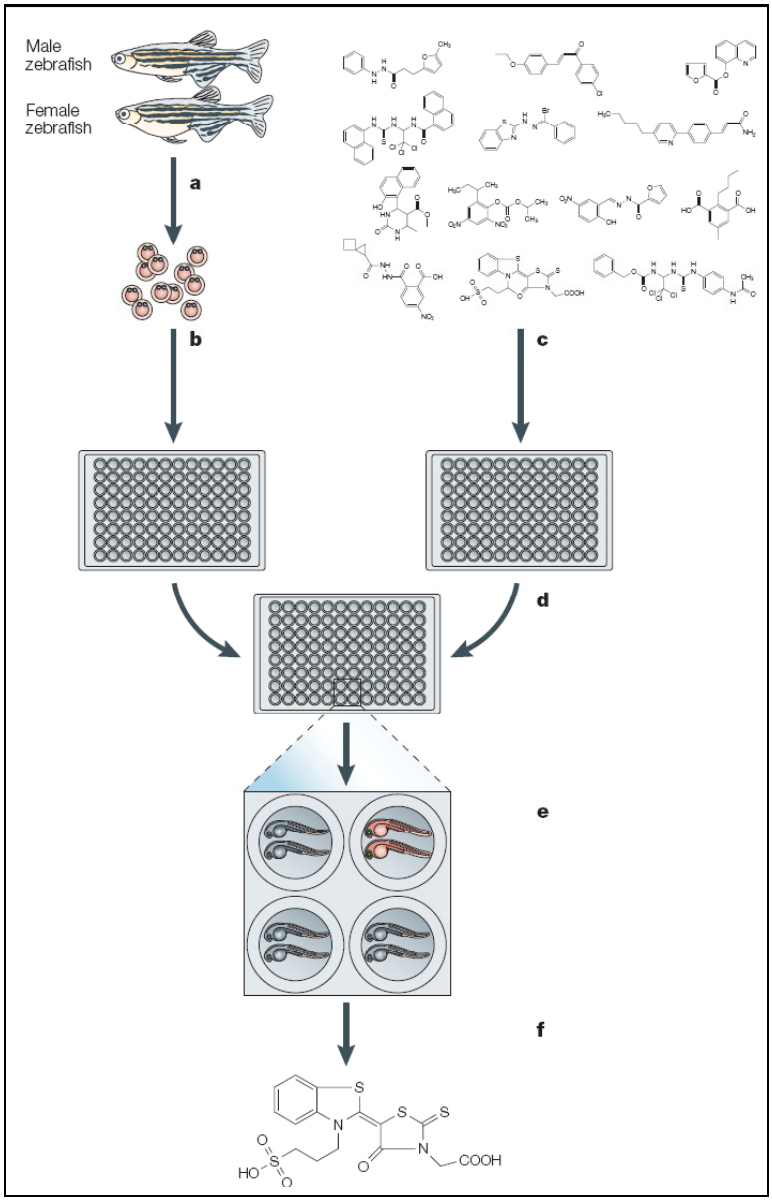



**Figure 4.4** *Zebrafish small-molecule screens.*[164]

a) Adult zebrafish are mated, producing 200-300 embryos. b) Embryos are distributed to 96-well plates, 2-3 per well. c) A small molecule library is acquired or synthesised. d) Small molecules are added to the embryonic medium. e) After incubation at 28.5 $^{o}$C, phenotypes are visually determined. f) Referral to the library database reveals the identity of bioactive small molecules.

### 4.3.2 Developmental stages of zebrafish embryos

The development of embryonic wild-type zebrafish (as used in our screens) is illustrated in **Figure 4.5**.[174] At 48 hpf the embryo hatches from its chorion and becomes a free swimming larvae that is sensitive to the touch. Anatomical terminology for the zebrafish is given in **Figure 4.6**.[173]


**Figure 4.5** *Stages of embryo development in zebrafish.*[174]

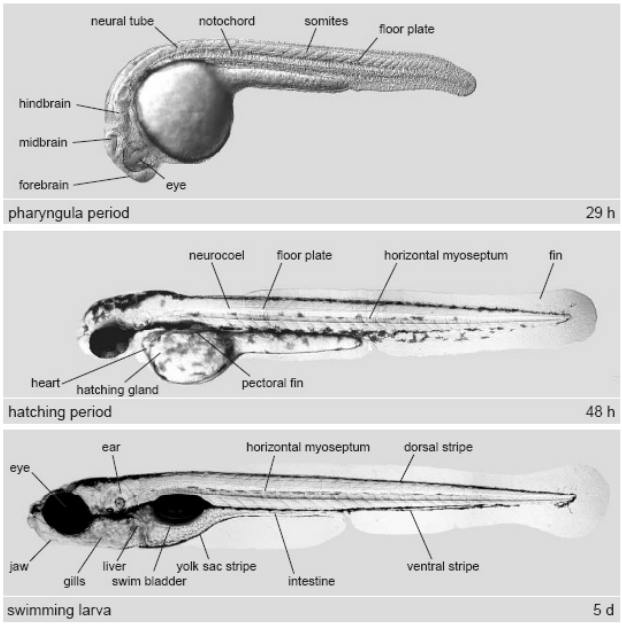



**Figure 4.6** *Anatomical terminology for zebrafish at 29 hpf, 48 hpf and 5 dpf.*[173]

### 4.3.3 Biological evaluation of our library using zebrafish phenotyping

In order to assess the applicability of our library to zebrafish screening, we proposed to carry out preliminary investigations using the diol hydrochloride mixtures **252-254**. If any activity was apparent then the individual component compounds of the mixture could be screened individually. For the substrates where no mixture was in hand, the three isolated diols were screened separately (naphthyl analogues **252e-254e**, parent analogues **252m-254m** and thiophene sulfonamide **256-258**). Using the procedure described in **section 4.3.1**, 'high stage' embryos (approximately 3-4 hpf) were treated with aliquots of the appropriate drug solution (all 0.5% $^{v}/_{v}$ DMSO in E3 medium), ranging in concentration from 10-100 μM for the mixtures, and 1-50 μM for the isolated compounds.

Several of the compounds/compound mixtures induced general symptoms of ill health in the fish. One such example was 5-methoxy compound mixture **252c-254c** that induced the bent tail phenotype in 5 dpf larvae at 50 μM (**Figure 4.7**, **a**). When mixture **252c-254c** was split out into its component compounds for a secondary assay, compound **254c** ($\Delta^{3,4}$ isomer) was found to result in extended tail length in 5 dpf zebrafish, at a concentration of 100 μM (**Figure 4.7**, **c**).

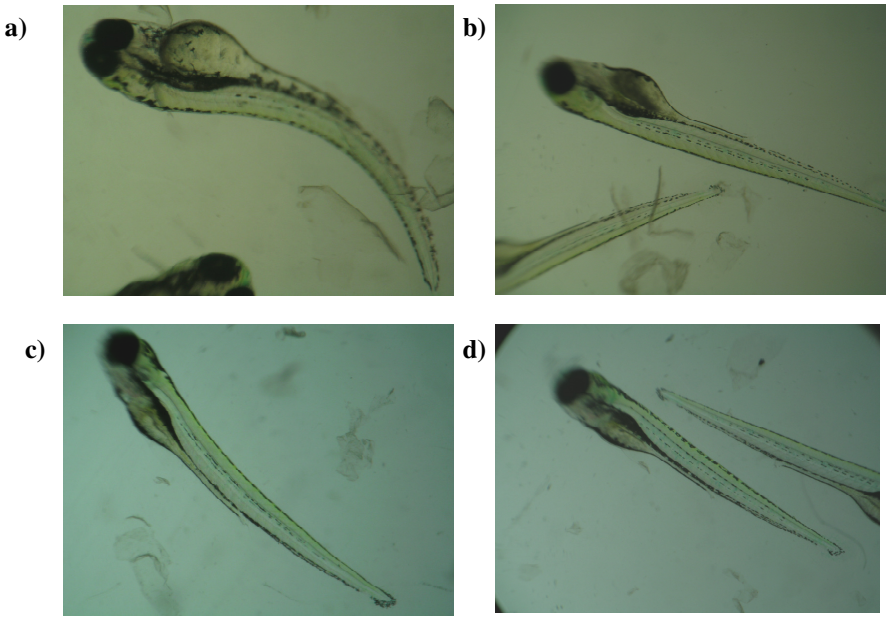



**Figure 4.7** *Tail modification using **252c-254c*** at 5 dpf.

a) 50 μM **252c-254c**. b) control; c) 100 μM **254c**; d) control.

One other example of general toxicity was shown for parent compound **253m** ($\Delta^{2,3}$ isomer) that was screened separately from the outset. This compound reproducibly induced oedema in the zebrafish at 50 µM, though no abnormal effects were shown above or below this concentration. **Figure 4.8** illustrates the enlarged heart and hatching gland at 2 dpf (**a**), increasing to the grossly enlarged yolk sack and heart, visible at 5 dpf (**c**, **e**).

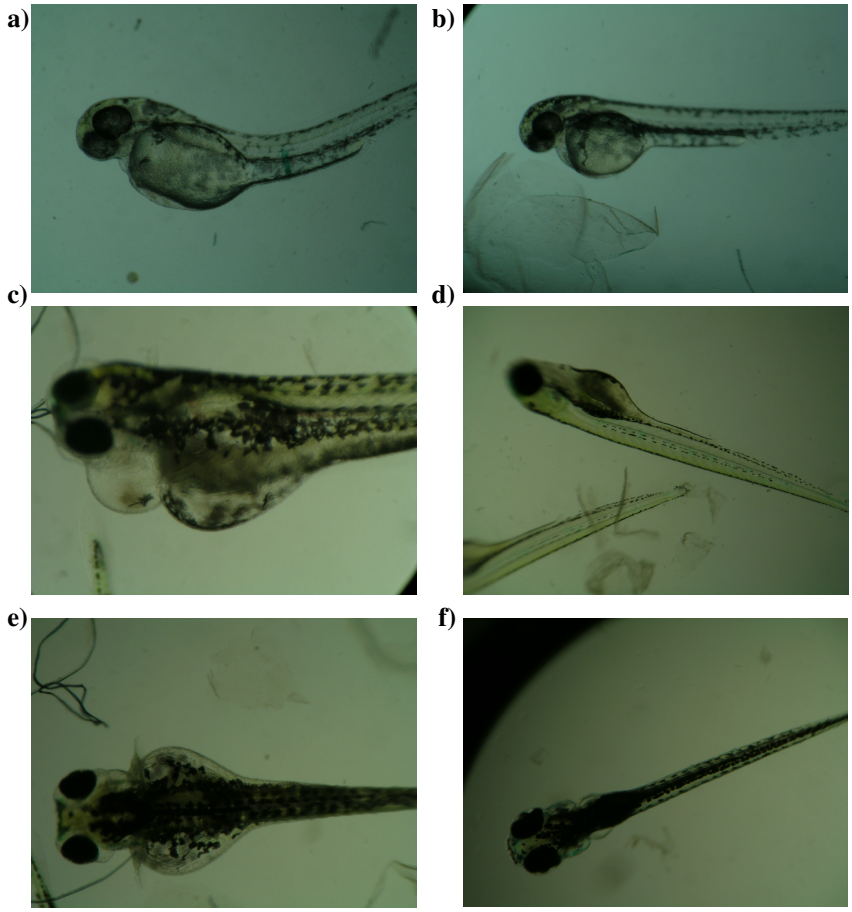



**Figure 4.8** *Generation of oedema by compound **253m**.*

a) 50 µM **253m**, 2 dpf; b) control, 2 dpf; c) 50 µM **253m**, 5 dpf, side view; d) control, 5 dpf, side view; e) 50 µM **253m**, 5 dpf, top view; f) control, 5 dpf, top view.

While these symptoms illustrated a level of toxicity associated with the appropriate compound/compounds, no dose dependence was shown and no tissue specificity was deduced since the general function of the organism was not altered overall. However, for fluorinated compound mixture **252b**-**254b** we did observe more severe effects, with reproducible embryo death at 50 µM, after 1 dpf (**Figure 4.9**, **a**).

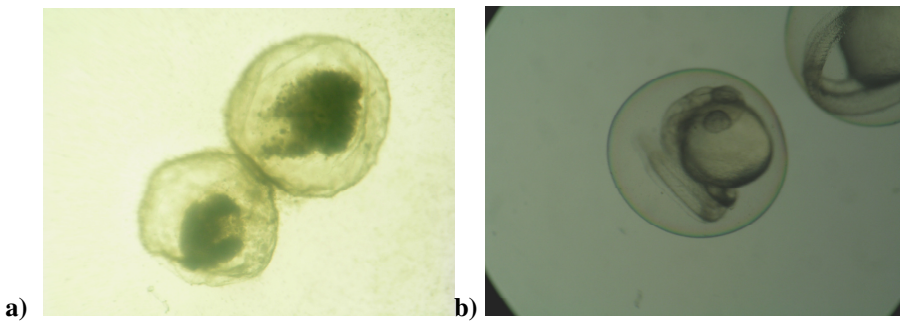



**Figure 4.9** *Dead embryos after exposure to 50 µM* ***252b-254b****.*

a) 50 µM **252b**-**254b**, 1 dpf; b) control, 1 dpf.

Although no effect was observed at the higher dose of 100 µM, the 50 µM results prompted us to screen compounds **252b**, **253b** and **254b** individually. For compounds **253b** and **254b** we observed no abnormalities, however compound **252b** ($\Delta^{1,2}$ isomer) appeared to slow down the development of the embryos significantly, and in a dose dependent manner (**Figure 4.10**).

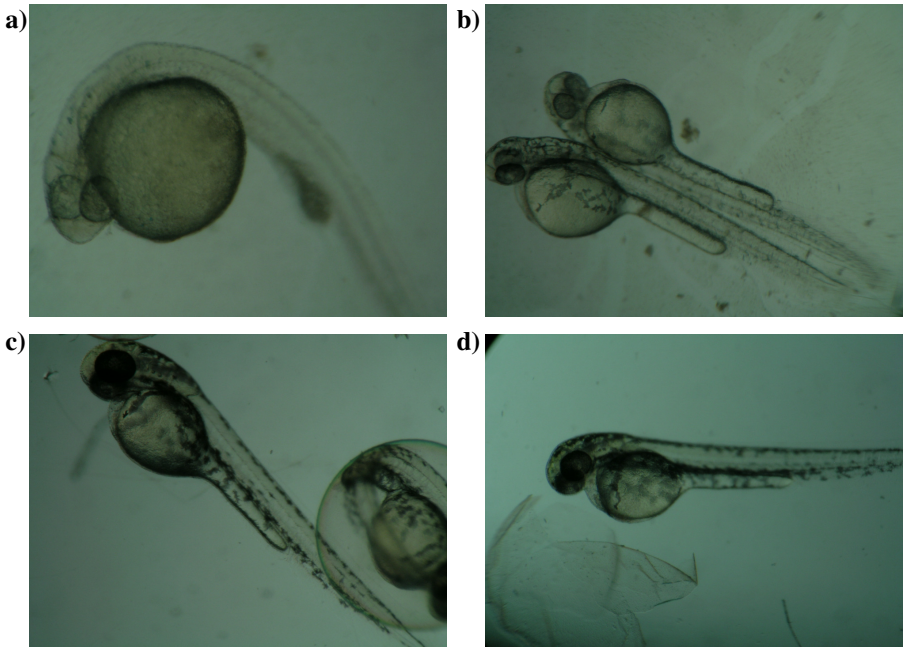



**Figure 4.10** *Delayed development of zebrafish embryos treated with* ***252b*** *at 2 dpf.*

All photos at 2 dpf. a) 100 µM **252b**; b) 50 µM **252b**; c) 20 µM **252b**; d) control.

At 5 dpf, the yolk sack of the fish treated with 100 µM **252b** was significantly larger than that of the control, providing further evidence for delayed development. Additionally the positioning of the melanocytes (pigmentation) on the underside of

the yolk sack was noticeably different from that of the control (**Figure 4.11**, **a**&**b**). The fish treated with 50 µM **252b** showed the bent tail phenotype reported previously (**Figure 4.7**), but no notable difference from the control was observed in the fish exposed to lower drug concentrations at 5 dpf.

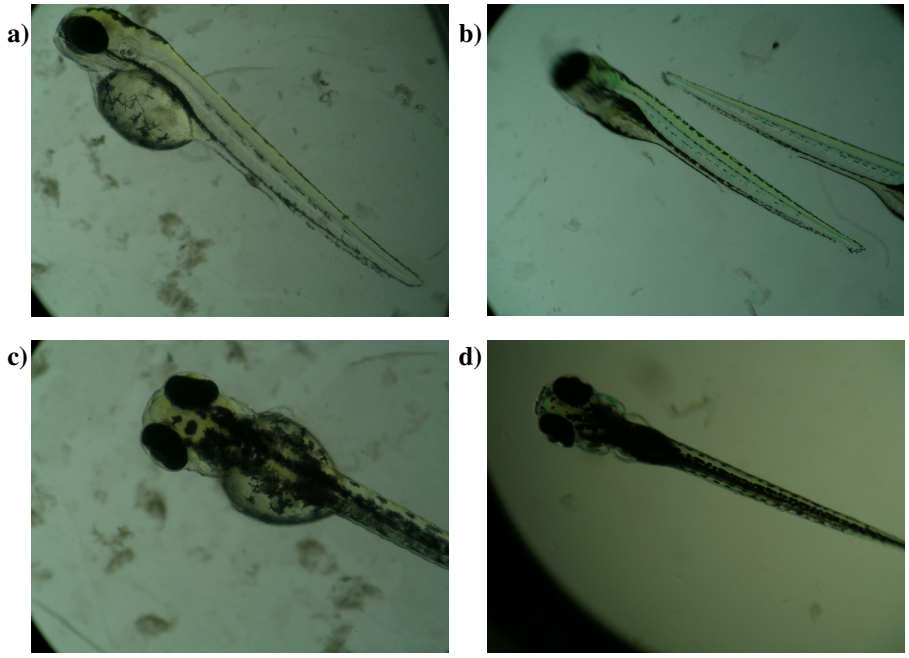



**Figure 4.11** *Delayed development of zebrafish embryos treated with **252b** at 5 dpf.*
All photos at 5 dpf. a) 100 µM **252b**, side view; b) control, side view; c) 100 µM **252b**, top view; d) control, top view.

The results obtained for compound **252b** are preliminary and require further investigation and replication on a larger scale to be of statistical significance. However, that being said, a decreased rate of embryo development and dose-dependence was clearly observed in our experiment. This suggests that compound **252b** interferes in some way with the cell division process (mitosis). This would be in agreement with the activity of the benzophenanthridine alkaloid chelidonine **76** that bears structural similarities to compound **252b** (**Figure 4.12**). Chelidonine **76** is known to cause mitotic arrest and inhibition of tubulin polymerisation, as well as being the major component of Ukrain™ **259**, a selectively toxic agent to malignant cells.[175] Further studies of compound **252b** using both zebrafish assays and cell-based techniques would enable a more probing identification of its specific mode of action.

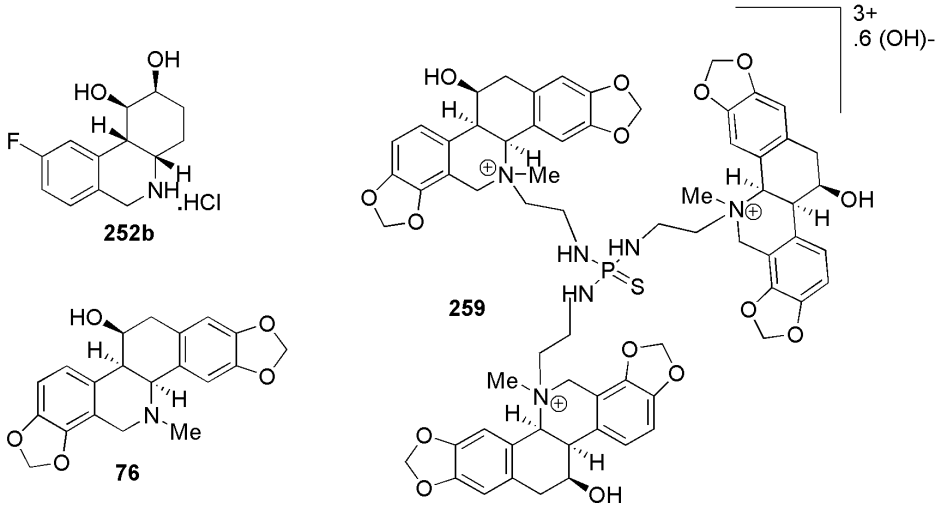



**Figure 4.12** *Chelidone **76** and Ukrain™ **259**.*[175]

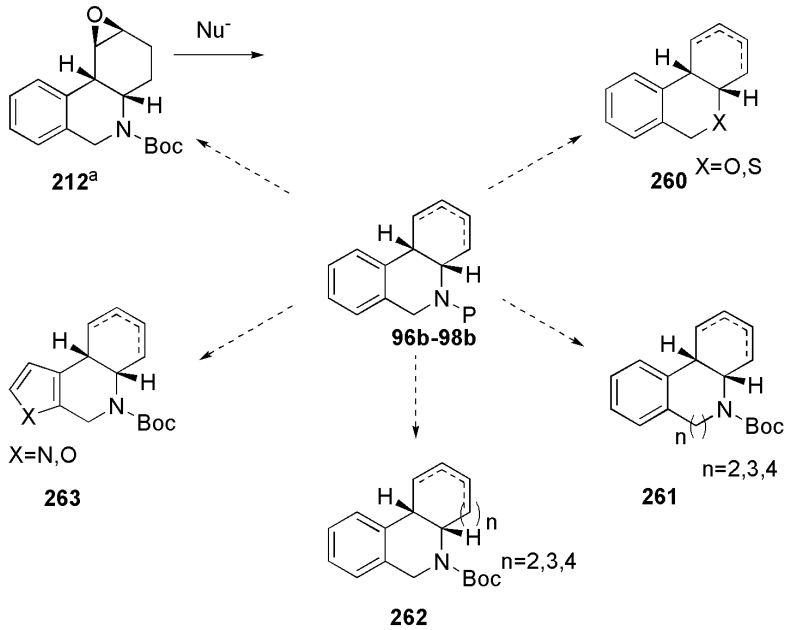
The remaining compounds/compound mixtures showed no specific phenotype upon application to the zebrafish embryos. However, as previously mentioned, zebrafish assays should be used in conjunction with standard cell-based techniques to provide a more accurate assessment of any potential bioactivity.[171]

### 4.4 Conclusion

The methodology developed in **Chapters 2** and **3** was successfully applied to the synthesis of a small library of dihydroxylated phenanthridines. Biological evaluation was facilitated using whole organism phenotype screening with zebrafish embryos. Preliminary results suggest that 5-methoxy analogue **254c** and phenyl analogue **253m** induce signs of ill health in the developing embryos, but the phenotype they induce does not indicate any tissue specificity. 4-Fluoro analogue **252b** was successfully shown to delay the zebrafish embryo development in a dose-dependent manner. Further evaluation of compound **252b** using more advanced zebrafish assays and cell-based techniques would enable the specific mode of action to be probed.

# FUTURE WORK
## CHAPTER FIVE

The synthesis of a small library of phenanthridines was successfully achieved using the methodology described in **Chapters 2**, **3** and **4**. This methodology could be extended to allow the incorporation of greater diversity, as illustrated in **Scheme 5.1**. The synthesis of oxygen and sulfur analogues such as **260** could be investigated using benzyl alcohol and benzyl thiol building blocks. Studies into the synthesis of a 7-membered B-ring derivative could be completed, and this methodology extended to incorporate 8- and 9-membered analogues such as **261**. Alternatively, the synthesis of larger C-ring derivatives such as **262** might be realised by the use of larger cycloalkenyl bromide building blocks. Studies into the incorporation of heteroaryl building blocks would yield further skeletal variation. In particular, thiophene analogues **158-160** and **195f-197f** are good precedent for the synthesis of pyrrole and furan equivalents such as **263**. Finally, further optimisation of the epoxidation step would furnish **212** on a scale appropriate for the study a variety of nucleophile-promoted ring-opening reactions.




**Scheme 5.1** *Further incorporation of diversity into the phenanthridine library.*

[a] Only the $\Delta^{1,2}$-isomer epoxide isomer product is shown for simplicity.

The results obtained for the RRM studies (**Chapter 3**) also warrant further investigation. It would be interesting to examine the application of the RRM reaction to less strained ring systems, such as the equivalent *trans*-ring fused phenanthridines, or other *trans*-ring fused substrates. This would allow us to determine if the reactivity of our propargylated phenanthridines **97f** and **98f** was a result of their strained conformation. Additionally, application of the RRM reaction to other *cis*-ring fused systems would allow the evaluation of RRM as a general tool for the modification of cyclic systems of this type.

The preliminary results from the biological screening of our phenanthridine library using zebrafish are promising (**Chapter 4**). So far the screening has only been performed on a small scale using 2-3 fish per compound, per assay. A larger scale experiment using 20 fish would permit a more accurate assessment of the effect of our most active analogue **252b**. Additionally, the effect of compound **252b** could be examined using yeast cell assays, which may also allow us to tie down the specific biological pathway that the compound is acting upon.

# EXPERIMENTAL
# CHAPTER 6

## EXPERIMENTAL PROCEDURES

### 6.1 General experimental

$^{1}H$ nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the indicated reference at the stated temperature on Varian Gemini 200 (200 MHz), Bruker AC250 (250 MHz), Bruker DPX360 (360 MHz), Bruker DMX500 (500 MHz), Bruker AVA600 (600 MHz) and Bruker AVA800 (800 MHz) instruments. The data is presented as follows: chemical shift (in ppm on the δ scale relative to $\delta_{TMS} = 0$), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, td = triplet of doublets, dd = doublet of doublets, dt = doublet of triplets, br = broad), coupling constants (in Hertz, Hz) and interpretation. $^{13}C$ NMR spectra were recorded at the stated temperature on Bruker AC250 (62.9 MHz), Bruker DPX360 (90.6 MHz), Bruker DMX500 (125.7 MHz), Bruker AVA600 (151.1 Hz) and Bruker AVA800 (201.5 Hz) instruments. Assignments are made on the basis of DEPT 135, DEPT 90 and 2D HSQC experiments.

Infra-red spectra were recorded using a Biorad FTS-7 or Perkin-Elmer Paragon 1000 FT-IR spectrometer as thin films unless otherwise stated. The wavelengths of maximum absorbance ($\upsilon_{max}$) are quoted in $cm^{-1}$. Electron impact (EI) mass spectra were obtained using a Finnigan 4500 mass spectrometer, and electrospray (ESI) and fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS50TC mass spectrometer. The parent ion, or relevant fragments are quoted, followed by significant fragments and their relative intensities. Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. TLC was carried out using Merk silica gel $60F_{254}$ foil-backed plates with visualisation by

ultraviolet and $KMnO_4$ (aq)[ϕ] and/or molybdate stain.[φ] Flash chromatography was carried out using Merck Kieselgel 60 (Merck 9385) under positive pressure by means of an airline or hand pump. Eluent compositions are quoted as $^{v}/_{v}$ ratios. High performance liquid chromatography (HPLC) was carried out using a Gilson instrument using a Spherisorb column (internal diameter: 20 mm) and fitted with a Gilson refractive index detector. Flow rates are a quoted for each separation in ml/min. All solvents used for HPLC were filtered prior to use and all HPLC samples were filtered through 0.45 μM nylon syringes prior to analysis.

All reactions non-aqueous were carried out under an atmosphere of nitrogen using flame- or oven-dried glassware that was cooled in a dessicator prior to use. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. Dichloromethane ($CH_2Cl_2$), triethylamine ($Et_3N$) and diisopropylethylamine ($^{i}Pr_2NEt$) were distilled from calcium hydride and stored over calcium hydride under a nitrogen atmosphere. When used as a reagent, dimethylformamide (DMF) was also distilled from and stored over calcium hydride under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium/benzophenone and stored under a nitrogen atmosphere. Diethyl ether ($Et_2O$), toluene and methanol (MeOH) were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com. Anhydrous dimethylacetamide (DMA), DMF (when used as a solvent) and acetonitrile (MeCN) were used as supplied by BakerDRY. Extra dry acetone was used as supplied by Acros. Anhydrous 1,4-dioxane was used as supplied by Aldrich. Saturated aqueous solutions of inorganic salts are represented as (volume, sat. aq.)

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[ϕ] Potassium permanganate dip prepared as follows: To water (1000 ml) was added $KMnO_4$ (10 g), $K_2CO_3$ (50 g) and NaOH (40 pellets). The mixture was stirred until the solid had dissolved.

[φ] Ammonium molybdate dip prepared as follows: To water (950 ml) was added concentrated sulphuric acid (50 ml), ammonium molybdate (50 g) and ceric sulfate (3 g). The mixture was stirred until all solid material had disappeared and a bright yellow solution remained.

The apparatus used for flash vacuum pyrolysis (FVP) is illustrated in **Figure 3.10**. The system was evacuated by use of an Edwards Model ED100 high capacity oil pump to maintain the pressure in the region of 0.030 Torr. A glass Büchi oven was used to heat the inlet tube in which the substrate was placed until it volatilises. The gaseous substrate passed through a silica tube (30 x 2.5 cm) heated by a Carbolite electronically controlled laboratory tube furnace (model number MTF 12/38/250). The estimated contact time in the hot zone is of the order of ten milliseconds and the gaseous phase of the substrate under vacuum ensures that intramolecular reactions are strongly favoured. The products are captured at the exit of the furnace in a U-shaped trap cooled in liquid nitrogen. Upon completion of the reaction the pump is isolated and the trap is allowed to warm to room temperature under a dry nitrogen atmosphere. Standard pyrolysis parameters used in this section are furnace temperature $T_f$, inlet temperature $T_i$, pressure $P$ and time of pyrolysis $t$.

**Index for General Procedures.**

## 6.2 Experimental for Chapter two

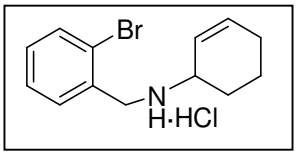
### General procedure A - Secondary amine formation

To a suspension of the appropriate 2-halobenzylamine hydrochloride (1 eq) in MeCN at 0 $^{o}$C was added $^{i}Pr_2NEt$ (4 eq) and the reaction was stirred for 5 mins. 3-Bromocyclohexene (1 eq) was added and the reaction stirred for 16 h at r.t. The reaction was concentrated under reduced pressure and the residue taken up in $CH_2Cl_2$ (50 ml) and washed with NaCl (3 x 50 ml, sat. aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2$, HCl (excess, 1.0 M in $Et_2O$) added and the resultant suspension filtered to afford the desired amine hydrochloride.

### General procedure B - Sulfonamide protection

To a solution of the appropriate amine or amine hydrochloride (1 eq) in $CH_2Cl_2$ (10 ml) at 0 $^{o}$C was added methanesulfonyl chloride (3 eq) and $Et_3N$ (3 eq) and the reaction was warmed to r.t. and stirred for 16 h. The reaction was diluted with $CH_2Cl_2$ (20 ml), and washed with HCl (3 x 20 ml, 1 M aq.). The organics were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography to afford the desired sulfonamide.

***N*-(2-Bromo-benzyl)-cyclohex-2-enyl-amine hydrochloride 93**

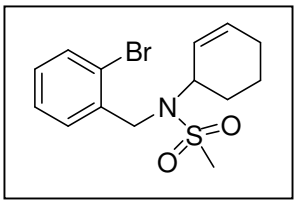



General procedure **A** was followed using 2-bromobenzylamine hydrochloride (6.00 g, 27.0 mmol), MeCN (100 ml), $^{i}Pr_2NEt$ (18.8 ml, 108 mmol), 3-bromocyclohexene (3.10 ml, 27.0 mmol), and HCl (30 ml, 1.0 M in $Et_2O$, 30.0 mmol) to afford amine hydrochloride **93** as a colourless solid (7.15 g, 99%).

**MP** 142 $^{o}$C ($Et_2O$); **$^{1}$H NMR** δ (250 MHz, $CD_3OD$) 7.79 (1H, dd, *J* 8.0, 1.3, Ar*H*), 7.66 (1H, dd, *J* 7.6, Ar*H*), 7.53 (1H, td, *J* 7.6, 1.3, Ar*H*), 7.43 (1H, td, *J* 7.9, 1.7, Ar*H*), 6.29-6.23 (1H, m, C*H*=CH), 5.91-5.87 (1H, m, CH=C*H*), 4.46 (2H, s, C$H_2$Ar), 4.06-4.03 (1H, m, C*H*N), 2.28-2.18 (3H, s, C$H_A$H$_B$+C$H_2$), 1.94-1.87 (3H, m, CH$_A$$H_B$+C$H_2$); **$^{13}$C NMR** δ (250 MHz, $CD_3OD$) 135.4 (CH), 133.0 (CH), 131.6 (CH), 131.1 (CH), 130.9 (C), 128.0 (CH), 124.5 (C), 120.7 (CH), 54.3 (CH), 46.9 ($CH_2$), 24.8 ($CH_2$), 23.9 ($CH_2$), 18.8 ($CH_2$); ***m/z*** (FAB, THIOG) 266 ([$^{81Br}$M-H]$^{+}$, 86 %), 264 ([$^{79Br}$M-H]$^{+}$, 70), 262 (27), 239 (25), 238 (28.5), 186 (91), 184 (88) ; **HRMS** (FAB, THIOG) Found: [$^{81Br}$M-H]$^{+}$, 266.0372. $C_{13}H_{15}N^{81}Br$ requires 266.0369. Found: [$^{79Br}$M-H]$^{+}$, 264.0383. $C_{13}H_{15}N^{79}Br$ requires 264.0388.

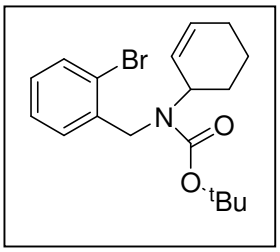
**Free Amine: $R_f$** [hexane:EtOAc, 3:1] = 0.90; **$\upsilon_{max}$** ($CH_2Cl_2$)/cm$^{-1}$ 3361 (NH), 1466, 1436, 1010, 747; **$^{1}$H NMR** δ (250 MHz, $CDCl_3$) 7.68 (1H, dd, *J* 7.9, 1.3, Ar*H*), 7.60 (1H, dd, *J* 7.7, 1.7, Ar*H*), 7.43 (1H, td, *J* 7.4, 1.1, Ar*H*), 7.26 (1H, td, *J* 7.6, 1.8, Ar*H*), 5.97-5.87 (2H, m, CHNC*H*=C*H*), 4.10 (1H, d, *J* 13.8, C$H_X$H$_Y$Ar), 4.03 (1H, d, *J* 13.8, CH$_X$$H_Y$Ar), 3.38 (1H, br s, C*H*N), 2.17-1.66 (6H, m, 3xC$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 139.5 (C), 132.5 (CH), 130.0 (CH), 129.6 (CH), 128.9 (CH), 128.2 (CH), 127.2 (CH), 123.7 (C), 52.3 (CH), 50.8 ($CH_2$), 29.2 ($CH_2$), 25.1 ($CH_2$), 19.9 ($CH_2$).

***N*-(2-Bromo-benzyl)-*N*-cyclohex-2-enyl-methanesulfonamide 94a**




General procedure **B** was followed using amine hydrochloride **93** (3.90 g, 14.6 mmol), $CH_2Cl_2$ (50 ml), $Et_3N$ (6.20 ml, 43.8 mmol) and methanesulfonyl chloride (3.40 ml, 43.8 mmol). Flash chromatography ($CH_2Cl_2$-$CH_2Cl_2$:MeOH, 100:1) afforded sulfonamide **94a** as a colourless solid (4.95 g, 99%). **$R_f$** [hexane:EtOAc, 3:1] = 0.46; **MP** 100 °C ($Et_2O$); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1332 ($SO_2$), 1145 ($SO_2$); **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.67 (1H, dd, *J* 7.8, 0.8, Ar*H*), 7.49 (1H, dd, *J* 7.9, 1.2, Ar*H*), 7.33 (1H, td, *J* 7.7, 1.2, Ar*H*), 7.12 (1H, m, Ar*H*), 5.98-5.93 (1H, m, NCHC*H*=CH), 5.53-5.47 (1H, m, NCHCH=C*H*), 4.66-4.57 (1H, m, NC*H*), 4.47 (1H, dd, *J* 17.7, C$H_X$$H_Y$Ar), 4.33 (1H, d, *J* 17.7, C$H_X$$H_Y$Ar), 2.97 (3H, s, C$H_3$), 1.99-1.92 (3H, m, C$H_A$$H_B$+C$H_2$), 1.70-1.34 (3H, m, C$H_A$$H_B$+C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 137.7 (C), 133.7 (CH), 132.1 (CH), 129.2 (CH), 128.4 (CH), 127.3 (CH), 126.5 (CH), 121.9 (C), 55.6 (CH), 47.5 ($CH_2$), 39.4 ($CH_3$), 28.7 ($CH_2$), 24.2 ($CH_2$), 21.4 ($CH_2$); ***m/z*** (FAB, THIOG) 346 ([$^{81Br}$M+H]$^+$, 64 %), 344 ([$^{79Br}$M+H]$^+$, 68), 266 (80), 264 (85); **HRMS** (FAB, THIOG) Found: [$^{81Br}$M+H]$^+$, 346.0326. $C_{14}H_{19}NO_2S^{81}Br$ requires 346.0301. Found: [$^{79Br}$M+H]$^+$ 344.0346. $C_{14}H_{19}NO_2S^{79}Br$ requires 344.0320.

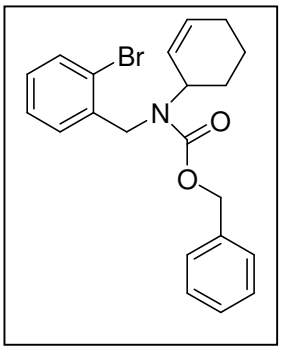
**(2-Bromo-benzyl)-cyclohex-2-enyl-carbamic acid *tert*-butyl ester 94b**




To a suspension of amine **93** (500 mg, 1.87 mmol) in $CH_2Cl_2$ (20 ml) was added $Et_3N$ (395 µl, 2.81 mmol). After 10 mins, the reaction was cooled to 0 °C, $Boc_2O$ (613 mg, 2.81 mmol) in $CH_2Cl_2$ (5 ml) was added and the reaction was stirred for a further 10 mins. The reaction was warmed to r.t and stirred for 16 h. The reaction was diluted with $CH_2Cl_2$ (20 ml), extracted with NaCl (3 x 20 ml, sat. aq.), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane:EtOAc:$Et_3N$, 10:1:0.1) afforded Boc amine **94b** as a colourless solid (685 mg, 90%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.8; **MP** 81 °C (hexane); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3057, 3021, 1695 (C=O), 1274, 1253; **$^1$H NMR** δ (360 MHz, 318 K, $CDCl_3$) 7.51 (1H, d, *J* 7.7, Ar*H*), 7.29-7.26 (2H, m, 2xAr*H*), 7.11-7.07 (1H, m, Ar*H*), 5.83 (1H, br s, C*H*=CH), 5.50 (1H, d, *J* 10.1, CH=C*H*), 4.90 (1H, br s, NC*H*), 4.38 (2H, br s, $CH_2$Ar), 2.10-1.81 (3H, m, $CH_2$+$CH_AH_B$), 1.81-1.70 (1H, m, $CH_AH_B$), 1.55-1.46 (2H, m, $CH_2$), 1.35 (9H, s, $3CH_3$); **$^{13}$C NMR** δ (90.6 MHz, 318 K, $CDCl_3$) 155.6 (C), 132.2 (CH), 131.7 (CH), 130.8 (C), 128.0 (CH), 127.7 (CH), 127.3 (CH), 126.9 (CH), 121.9 (C), 79.7 (C), 53.0 (CH), 52.6 ($CH_2$), 28.0 ($3xCH_3$), 27.3 ($CH_2$), 24.4 ($CH_2$), 21.2 ($CH_2$); ***m/z*** (FAB, THIOG) 368 ([$^{81Br}$M+H]$^+$, 12 %), 366 ([$^{79Br}$M+H]$^+$, 15), 313 (33), 312 (68), 311 (39), 310 (70), 266 (28), 232 (57), 230 (51); **HRMS** (FAB, THIOG) Found: [$^{81Br}$M+H]$^+$ 368.1046. $C_{18}H_{25}NO_2{}^{81}Br$ requires 368.1050. Found: [$^{79Br}$M+H]$^+$ 366.1067. $C_{18}H_{25}NO_2{}^{79}Br$ requires 366.1069.

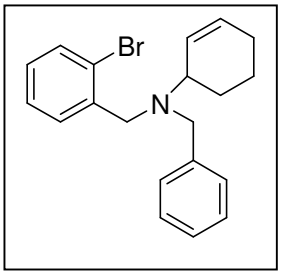
**(2-Bromo-benzyl)-cyclohex-2-enyl-carbamic acid benzyl ester 94c**




To a suspension of NaH (143 mg, 60% dispersion in mineral oil, 3.62 mmol) in DMF (10.0 ml) at 0 °C was added amine **93** (500 mg, 1.65 mmol) in DMF (10.0 ml). The solution was stirred for 30 mins then benzyl chloroformate (302 µl, 2.15 mmol) was added dropwise and the reaction was warmed to r.t. and stirred for 16 h. The reaction was diluted with $Et_2O$ (20 ml), extracted with NaCl (3 x 20.0 ml, sat. aq.), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Flash chromatography (hexane:EtOAc:$Et_3N$, 100:1:0.1–100:5:0.1) afforded Cbz amide **94c** as a colourless solid (570 mg, 86%).

**$R_f$** [hexane:EtOAc, 10:1] = 0.54; **MP** 48 °C (hexane); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3064, 3021, 1699, 1407, 1258; **$^1$H NMR** δ (360 MHz, 323K, $CDCl_3$) 7.52 (1H, d, *J* 5.8, Ar*H*), 7.40 – 7.22 (7H, m, 7xAr*H*), 7.11-7.08 (1H, m, ArH), 5.87-5.85 (1H, m, C*H*=CH), 5.48 (1H, d, *J* 10.2, CH=C*H*), 5.16 (2H, br s, OC$H_2$Ar), 4.89 (1H, br s, C*H*N), 4.51 (1H, d, *J* 17.4, C$H_X$H$_Y$Ar), 4.44 (1H, d, *J* 17.4, CH$_X$$H_Y$Ar), 2.11-1.84 (3H, m, C$H_2$+C$H_A$H$_B$), 1.80-1.70 (1H, m, CH$_A$$H_B$), 1.70-1.47 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, 323K, $CDCl_3$) 156.4 (C), 138.4 (C), 136.7 (C), 132.4 (2xCH), 128.3 (CH), 127.9 (CH), 127.7 (3xCH), 127.6 (3xCH), 127.1 (CH), 122.1 (C), 67.3 ($CH_2$), 53.8 (CH), 47.7 ($CH_2$), 28.1 ($CH_2$), 24.5 ($CH_2$), 21.2 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 402 ([$^{81Br}$M+H]$^+$, 35 %), 400 ([$^{79Br}$M+H]$^+$, 38), 310 (22), 308 (22), 171 (69), 169 (50) ; **HRMS** (FAB, THIOG) Found: [$^{81Br}$M+H]$^+$ 402.0821. $C_{21}H_{23}O_2{}^{81}$BrN requires 402.0979. Found: [$^{79Br}$M+H]$^+$ 400.0918. $C_{21}H_{23}O_2{}^{79}$BrN requires 400.0912.

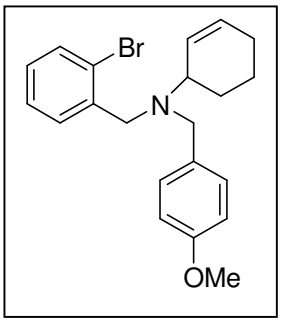
**Benzyl-(2-bromo-benzyl)-cyclohex-2-enyl-amine 94d**




To a suspension of amine **93** (750 mg, 2.47 mmol) in DMF (20 ml) at 0 $^{o}$C, was added NaH (217 mg, 60% dispersion in mineral oil, 5.43 mmol) and the reaction stirred for 30 mins. Benzyl bromide (382 µl, 3.21 mmol) was added dropwise and the reaction warmed to r.t and stirred for 16 h. $Et_2O$ (20 ml) was added and the organics washed with NaCl (3 x 30 ml, sat. aq.), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc:$NH_3$, 100:1:0.1) to afford benzylamine **94d** as a colourless oil (712 mg, 81%).

**$R_f$** [hexane] = 0.29; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3057, 3019, 1026; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.71 (1H, dd, *J* 7.7, 1.6, Ar*H*), 7.49 (1H, dd, *J* 8.0, 1.2, Ar*H*), 7.40 (2H, d, *J* 7.4, 2xAr*H*), 7.31-7.27 (3H, m, 3xAr*H*), 7.27-7.21 (1H, m, Ar*H*), 7.07 (1H, td, *J* 7.9, 1.8, Ar*H*), 5.89-5.84 (1H, m, C*H*=CH), 5.79 (1H, d, *J* 10.4, CH=C*H*), 3.81 (1H, d, *J* 15.3, C$H_P$H$_Q$Ar), 3.78 (1H, d, *J* 14.0, C$H_X$H$_Y$), 3.75 (1H, d, *J* 15.3, CH$_P$$H_Q$), 3.63 (1H, d, *J* 14.0, CH$_X$$H_Y$), 3.39-3.36 (1H, m, NC*H*), 2.08-1.95 (3H, m, C$H_2$+C$H_A$H$_B$), 1.85-1.76 (1H, m, CH$_A$$H_B$), 1.64-1.42 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 140.3 (C), 139.5 (C), 132.3 (CH), 130.4 (CH), 130.3 (CH), 130.2 (CH), 128.4 (2xCH), 128.0 (2xCH), 127.8 (CH), 127.2 (CH), 126.6 (CH), 124.0 (C), 55.2 (CH), 54.0 ($CH_2$), 53.1 ($CH_2$), 25.2 ($CH_2$), 23.5 ($CH_2$), 21.7 ($CH_2$) ; ***m/z*** (FAB, THIOG) 356 ([$^{81Br}$M+H]$^+$, 52 %), 354 ([$^{79Br}$M+H]$^+$, 47 %), 329 (35), 327 (35), 276 (75), 274 (53), 184 (34), 171 (69), 169 (71); **HRMS** (FAB, THIOG) Found: [$^{81Br}$M+H]$^+$ 356.0838. $C_{20}H_{23}NO_2{}^{81}Br$ requires 356.0838. Found: [$^{79Br}$M+H]$^+$ 354.0856. $C_{20}H_{23}N^{79}Br$ requires 354.0857.

**(2-Bromo-benzyl)-cyclohex-2-enyl-(4-methoxy-benzyl)-amine 94e**




To a suspension of amine **93** (750 mg, 2.81 mmol) in DMF (20 ml) at 0 $^{o}$C was added NaH (246 mg, 60% dispersion in mineral oil, 6.18 mmol) and the reaction was stirred until homogeneous. The reaction was warmed to r.t. and stirred for 30 mins, then cooled to 0 $^{o}$C, *p*-methoxybenzyl bromide (614 µl, 4.21 mmol) was added and the reaction stirred for 15 mins. The reaction was warmed to r.t. and stirred for 16 h. $Et_2O$ (30 ml) was added, the organics washed with NaCl (3 x 20 ml, sat. aq.), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc:$NH_3$, 100:1.5:0.1) to afford PMB protected amine **94e** as a colourless oil (912 mg, 84%).

**$R_f$** [hexane: EtOAc, 3:1] = 0.81; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2857, 1541, 1508, 1457, 1248, 750; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.69 (1H, d, *J* 7.8, Ar*H*), 7.47 (1H, dd, *J* 7.8, Ar*H*), 7.31-7.25 (3H, m, 3xAr*H*), 7.04 (1H, td, *J* 7.8, 1.7, Ar*H*), 6.83 (2H, dd, *J* 6.7, 1.8, 2xAr*H*), 5.85-5.82 (1H, m,C*H*=CH), 5.76 (1H, d, *J* 10.5, CH=C*H*), 3.76 (3H, s, OC$H_3$), 3.75 (2H, m, C$H_2$Ar), 3.70 (1H, d, *J* 13.8, C$H_X$H$_Y$Ar), 3.55 (1H, d, *J* 13.8, CH$_X$$H_Y$Ar), 3.34 (1H, br s, C*H*N), 2.04-1.93 (3H, m, CH$_2$C$H_A$H$_B$), 1.83-1.75 (1H, m, CH$_A$$H_B$), 1.58-1.48 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 158.3 (C), 139.6 (C), 132.2 (C), 132.1 (CH), 130.4 (CH), 130.1 (2xCH), 129.4 (2xCH), 127.7 (CH), 127.0 (CH), 123.9 (C), 113.4 (2xCH), 55.0 ($CH_3$), 54.9 (CH), 53.3 ($CH_2$), 52.9 ($CH_2$), 25.2 ($CH_2$), 23.4 ($CH_2$), 21.7 ($CH_2$) ; ***m/z*** (FAB, THIOG) 389 ([$^{81Br}$M+H]$^+$, 15 %), 387 ([$^{79Br}$M+H]$^+$, 43), 359 (53), 357 (54), 306 (43.9), 304 (41.2), 280 (21.8), 278 (24.4), 216 (35.9), 214 (21.0); **HRMS** (FAB, THIOG) Found: [$^{81Br}$M+H]$^+$ 388.1068. $C_{21}H_{24}NO^{81}Br$ requires 388.1100. Found: [$^{79Br}$M+H]$^+$ 386.1121. $C_{21}H_{24}NO^{79}Br$ requires 386.1120).

**General Procedures for Heck cyclisations**

**General procedure C**

**Cationic protocol:** To a degassed solution of the aryl halide (1 eq) in DMF was added palladacycle **100** (5 mol%) and $Ag_2CO_3$ (1 eq), and the reaction was heated at 140 °C. At the conclusion of the reaction (as judged by TLC), the mixture was allowed to cool and then diluted with $Et_2O$ (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.

**General procedure D**

**Neutral protocol (140 $^oC$):** To a degassed solution of the aryl halide (1 eq) in DMF was added palladacycle **100** (5 mol%) and $MeNCy_2$ (4 eq), and the reaction was heated at 140 °C. At the conclusion of the reaction (as judged by TLC), the mixture was allowed to cool and then diluted with $Et_2O$ (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.

**General procedure E**

**Neutral protocol (Low temperature):** To a degassed solution of the aryl halide (1 eq) and $MeNCy_2$ (4 eq) in MeCN was added $Pd_2(dba)_3$ (5 mol%) and $^tBu_3PHBF_4$ (10 mol %), and the reaction mixture stirred at r.t. (Method **A**) or or 50 $^oC$ (Method **B**) for the indicated time. At the conclusion of the reaction (as judged by TLC), the mixture was allowed to cool and then diluted with $Et_2O$ (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.

**Application of optimised methods in Table 2.6, 2.7 and 2.8**

**Sulfonamide-functionalised phenanthridine 96a-98a**

**(Table 2.6, Entry 1)** General procedure **C** was employed using sulfonamide **94a** (50 mg, 0.144 mmol), palladacycle **100** (8.1 mg, 8.6 µmol) and $Ag_2CO_3$ (40 mg, 0.144 mmol) in DMF (3 ml). After 70 mins at 140 °C, work up and column chromatography (hexane:EtOAc, 10:1–4:1) afforded the phenanthridine as a colourless oil (38 mg, 99%). $^1$H NMR of this oil showed it to be an 85:13:2 mixture of double bond isomers (**96a**:**97a**:**98a**).

**(Table 2.7, Entry 1)** General procedure **D** was employed using sulfonamide **94a** (50 mg, 0.144 mmol), palladacycle **100** (8.1 mg, 8.6 µmol) and $MeNCy_2$ (122 µl, 0.576 mmol) in DMF (3 ml). After 3h at 140 °C, work up and column chromatography (hexane:EtOAc, 10:1–4:1) afforded the phenanthridine as a colourless oil (37 mg, 99%). $^1$H NMR of this oil showed it to be an 44:31:25 mixture of double bond isomers (**96a**:**97a**:**98a**).

**(Table 2.8, Entry 1)** General procedure **E** (Method **A**) were employed using sulfonamide **94a** (50 mg, 0.144 mmol), $Pd_2(dba)_3$ (6.6 mg, 7.2 µmol), $^t$Bu$_3$PHBF$_4$ (4.2 mg, 14.4 µmol) and $MeNCy_2$ (122 µl, 0.576 mmol) in MeCN (3 ml). After 9 h at r.t, work up and column chromatography (hexane:EtOAc, 10:1–5:1) afforded the phenanthridine as a colourless oil (38 mg, 99%). $^1$H NMR of this oil showed it to be a 12:65:23 mixture of double bond isomers (**96a**:**97a**:**98a**).

**(Table 2.8, Entry 2)** General procedure **E** (Method **B**) was employed using sulfonamide **94a** (50 mg, 0.144 mmol), $Pd_2(dba)_3$ (6.6 mg, 7.2 µmol), $^t$Bu$_3$PHBF$_4$ (4.2 mg, 14.4 µmol) and $MeNCy_2$ (122 µl, 0.576 mmol) in MeCN (3 ml). After 4 h at 50 °C, work up and column chromatography (hexane:EtOAc, 10:1–5:1) afforded the phenanthridine as a colourless oil (38 mg, 99%). $^1$H NMR of this oil showed it to be a 54:41:4 mixture of double bond isomers (**96a**:**97a**:**98a**).

**Boc-functionalised phenanthridine 96b-98b**

**(Table 2.6, Entry 2)** General procedure **C** was employed using amide **94b** (96 mg, 0.26 mmol), palladacycle **100** (15 mg, 15.7 μmol) and $Ag_2CO_3$ (72 mg, 0.26 mmol) in DMF (6 ml). After 2 h at 140 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (74 mg, 99%). $^1$H NMR of this oil showed it to be an 83:15:2 mixture of double bond isomers (**96b:97b:98b**).

**(Table 2.7, Entry 2)** General procedure **D** was employed using amide **94b** (53 mg, 0.144 mmol), palladacycle **100** (7 mg, 7.2 μmol) and $MeNCy_2$ (122 μl, 0.576 mmol) in DMF (3 ml). After 3 h at 140 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (39 mg, 95%). $^1$H NMR of this oil showed it to be an 38:36:28 mixture of double bond isomers (**96b:97b:98b**).

**(Table 2.8, Entry 3)** General procedure **E** (Method **B**) was employed using amide **94b** (53 mg, 0.144 mmol), $Pd_2(dba)_3$ (6.6 mg, 7.2 μmol), $^t$Bu$_3$PHBF$_4$ (4.2 mg, 14.4 μmol) and $MeNCy_2$ (122 μl, 0.576 mmol) in MeCN (3 ml). After 7 h at 50 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (39 mg, 95%). $^1$H NMR of this oil showed it to be a 34:37:29 mixture of double bond isomers (**96b:97b:98b**).

**Cbz-functionalised phenanthridine 96c-98c**

**(Table 2.6, Entry 3)** General procedure **C** was employed using amide **94c** (100 mg, 0.25 mmol), palladacycle **100** (11.7 mg, 12.5 μmol) and $Ag_2CO_3$ (69 mg, 0.25 mmol) in DMF (6 ml). After 2 h at 140 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (86 mg, 99%). $^1$H NMR of this oil showed it to be a 92:6:2 mixture of double bond isomers (**96c:97c:98c**) .

**(Table 2.7, Entry 3)** General procedure **D** was employed using amide **94c** (58 mg, 0.144 mmol), palladacycle **100** (7 mg, 7.2 μmol) and $MeNCy_2$ (122 μl, 0.576 mmol) in DMF (3 ml). After 3 h at 140 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (44 mg, 99%). $^1$H NMR of this oil showed it to be a 33:29:28 mixture of double bond isomers (**96c:97c:98c**).

**(Table 2.8, Entry 6)** General procedure **E** (Method **B**) was employed using amide **94c** (58 mg, 0.144 mmol), $Pd_2(dba)_3$ (6.6 mg, 7.2 μmol), $^t$Bu$_3$PHBF$_4$ (4.2 mg, 14.4 μmol) and $MeNCy_2$ (122 μl, 0.576 mmol) in MeCN (3 ml). After 7 h at 50 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (39 mg, 85%). $^1$H NMR of this oil showed it to be a 36:5:59 mixture of double bond isomers (**96c:97c:98c**).

**Benzyl-functionalised phenanthridine 96d-98d**

**(Table 2.6, Entry 4)** General procedure **C** was employed using amine **94d** (100 mg, 0.29 mmol), palladacycle **100** (13.5 mg, 14.4 μmol) and $Ag_2CO_3$ (79 mg, 0.29 mmol) in DMF (6 ml). After 2 h at 140 °C, work up and column chromatography (hexane:EtOAc:$Et_3N$, 100:1:0–100:1:0.1) afforded the phenanthridine **96d** as a colourless oil (73 mg, 92%).

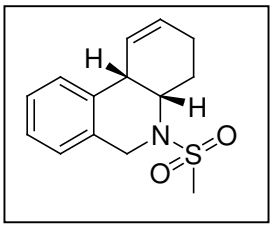
**(Table 2.7, Entry 4)** General procedure **D** was employed using amine **94d** (50 mg, 0.148 mmol), palladacycle **100** (7 mg, 7.4 μmol) and $MeNCy_2$ (126 μl, 0.592 mmol) in DMF (3 ml). After 5 h at 140 °C, work up and column chromatography (hexane:EtOAc:$Et_3N$, 100:1:0–100:1:0.1) afforded the phenanthridine as a colourless oil (37 mg, 93%). $^1$H NMR of this oil showed it be a 83:8:9 mixture of double bond isomers (**96d:97d:98d**).

**PMB-protected phenanthridine 96e-98e**

**(Table 2.6, Entry 5)** General procedure **C** was employed using amine **94e** (112 mg, 0.29 mmol), palladacycle **100** (13.5 mg, 14.4 μmol) and $Ag_2CO_3$ (79 mg, 0.29 mmol) in DMF (6 ml). After 160 mins at 140 °C, work up and column chromatography (hexane:EtOAc, 50:1-10:1) afforded the phenanthridine as a colourless oil (67 mg, 76%). $^1$H NMR of this oil showed it to be a 97:3:0 mixture of double bond isomers (**96e:97e:98e**).

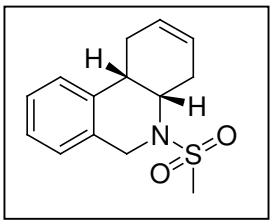
**(Table 2.7, Entry 5)** General procedure **D** was employed using amine **94e** (56 mg, 0.144 mmol), palladacycle **100** (7 mg, 7.2 μmol) and $MeNCy_2$ (122 μl, 0.576 mmol) in DMF (3 ml). After 5 h at 140 °C, work up and column chromatography (hexane:EtOAc, 50:1-10:1) afforded the phenanthridine as a colourless oil (41 mg, 93%). $^1$H NMR of this oil showed it to be a 74:13:13 mixture of double bond isomers (**96e:97e:98e**).

**(4a*SR*,10b*SR*)-5-Methanesulfonyl-3,4,4a,5,6,10b-hexahydro-phenanthridine 96a ($\Delta^{1,2}$ isomer)**



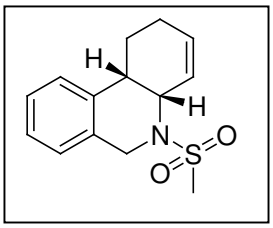
**$R_f$** [hexane:EtOAc, 3:1] = 0.38; **$R_t$** [hexane:EtOAc, 11:9] 15.9 mins; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3029, 1671, 1328, 1152; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.31 (1H, d, *J* 7.5, Ar*H*), 7.26 (1H, t, *J* 7.8, Ar*H*), 7.19 (1H, t, *J* 7.3, Ar*H*), 7.10 (1H, d, *J* 7.5, Ar*H*), 5.58 (1H, ddt, *J* 10.0, 4.8, 1.9, CHC*H*=CH), 5.86 (1H, dtd, *J* 10.0, 3.9, 1.7, CH=C*H*$CH_2$), 4.59 (1H, d, *J* 16.2, C$H_XH_Y$Ar), 4.43 (1H, d, *J* 16.2, C$H_XH_Y$Ar), 4.19 (1H, dt, *J* 8.4, 5.8, NC*H*CH), 3.66 (1H, br s, C*H*CH=CH), 2.74 (3H, s, C$H_3$), 2.27-2.20 (2H, m, C$H_2$), 1.87-1.81 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.0 MHz, $CDCl_3$) 136.9 (C), 131.1 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 126.7 (CH), 126.3 (CH), 125.9 (CH), 52.1 (CH), 44.1 ($CH_2$), 38.2 ($CH_3$), 37.4 (CH), 25.1 ($CH_2$), 24.0 ($CH_2$); ***m/z*** (FAB, THIOG) 264 ($[M+H]^+$, 19 %), 217 (25), 130 (79), 109 (38); **HRMS** (FAB, THIOG) Found: $[M+H]^+$ 264.1050. $C_{14}H_{18}NO_2S$ requires 264.1058. This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

**(4a*SR*,10b*SR*)-5-Methanesulfonyl-1,4,4a,5,6,10b-hexahydro-phenanthridine (97a) ($\Delta^{2,3}$ isomer)**



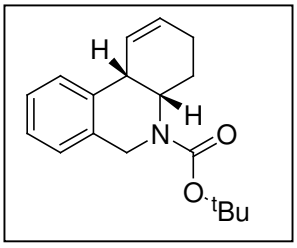
**$R_f$** [hexane:EtOAc, 3:1] = 0.32; **$R_t$** [hexane:EtOAc, 11:9] 18.1 mins; **MP** 140 $^oC$ (hexane); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.29-7.23 (3H, m, 3xAr*H*), 7.17 (1H, dd, *J* 6.5, 1.8, Ar*H*), 5.69-5.66 (1H, m, $CHCH_2$C*H*=), 5.42(1H, ddt, *J* 10.0, 5.1, 2.3, NCH$CH_2$C*H*=), 4.53 (2H, s, C$H_2$Ar), 4.29 (1H, ddd, *J* 10.4, 4.0, 2.4, NC*H*$CH_2$), 3.26-3.22 (1H, m, C*H*$CH_2$), 2.94 (3*H*, s, $CH_3$), 2.92-2.85 (1H, m, C$H_AH_B$), 2.69-2.58 (1H, m, $CH_AH_B$), 2.28-2.23 (1H, m, C$H_CH_D$), 1.80-1.71 (1H, m, $CH_CH_D$); **$^{13}$C NMR** δ (90.0 MHz, $CDCl_3$) 135.6 (C), 128.5 (C), 127.3 (CH), 126.5 (CH), 126.4 (CH), 125.3 (CH), 124.9 (CH), 123.8 (CH), 51.7 (CH), 45.0 ($CH_2$), 37.7 ($CH_3$), 35.8 (CH), 27.9 ($CH_2$), 26.5 ($CH_2$). This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

**(4a*SR*,10b*SR*)-5-Methanesulfonyl-1,2,4a,5,6,10b-hexahydro-phenanthridine (98a) ($\Delta^{3,4}$ isomer)**



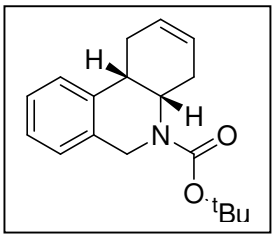
**$R_f$** [hexane:EtOAc, 3:1] = 0.39; **$R_t$** [hexane:EtOAc, 11:9] 15.4 mins; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.37 (1H, d, *J* 7.8, Ar*H*), 7.26 (1H, t, *J* 7.2, Ar*H*), 7.19 (1H, t, *J* 7.3, Ar*H*), 7.07 (1H, d, *J* 7.4, Ar*H*), 5.83-5.80 (1H, m, $CH_2CH$=CH), 5.61 (1H, dt, *J* 10.2, 1.0, CH=C*H*CH), 4.87-4.83 (1H, m, NC*H*), 4.59 (1H, d, *J* 16.5, $CH_XH_YAr$), 4.26 (1H, d, *J* 16.5, $CH_XH_YAr$), 3.39 (1H, br s, $CHCH_2$), 2.83 (3*H*, s, $CH_3$), 2.43-2.38 (1H, m, $CH_AH_B$), 2.05-1.97 (1H, m, $CH_AH_B$), 1.94-1.76 (2H, m, $CH_2CH$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 134.5 (C), 133.0 (CH), 132.4 (C), 127.3 (CH), 126.9 (CH), 126.1 (2xCH), 125.8 (CH), 52.4 (CH), 43.3 ($CH_2$), 39.8 ($CH_3$), 34.1 (CH), 25.3 ($CH_2$), 20.1 ($CH_2$). This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

**(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-3*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 96b ($\Delta^{1,2}$ isomer)**



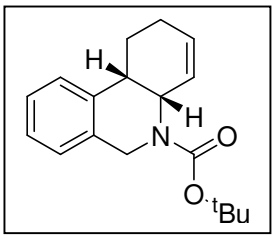
**$R_f$** [hexane:EtOAc, 10:1] = 0.42; **$R_t$** [hexane:EtOAc, 92:8] 17 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3026, 1693 (C=O), 1258, 913, 745; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.30 (1H, d, *J* 7.5, Ar*H*), 7.25-7.17 (2H, m, 2xAr*H*), 7.12 (1H, d, *J* 7.2, Ar*H*), 6.17-6.13 (1H, m, CHC*H*=CH), 5.87-5.83 (1H, m, CH=C*H*$CH_2$), 4.71 (1H, d, *J* 16.5, $CH_XH_YAr$), 4.41 (1H, br s, NC*H*CH), 4.39 (1H, d, *J* 16.5, $CH_XH_YAr$), 3.57 (1H, br s, NCHC*H*), 2.31-2.27 (1H, m, $CH_AH_B$), 2.15-2.05 (1H, m, $CH_AH_B$), 1.79-1.69 (1H, m, $CH_CH_D$), 1.61-1.40 (10H, m, 3 x $CH_3$+$CH_CH_D$); **$^{13}$C NMR** δ (90.0 MHz, 323 K, $CDCl_3$) 155.0 (C), 137.8 (C), 132.5 (C), 128.3 (CH), 128.1 (C), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.1 (CH), 125.9 (CH), 79.6 (C), 43.5 ($CH_2$), 37.3 (CH), 28.5 (3x$CH_3$), 25.3 ($CH_2$), 24.2 ($CH_2$); ***m/z*** (FAB, THIOG) 284 ($[M-H]^+$, 44 %), 228 (66), 184 (49), 130 (25); **HRMS** (FAB, THIOG) Found: $[M-H]^+$ 284.1643. $C_{18}H_{22}NO_2$ requires 284.1650.

**(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 97b ($\Delta^{2,3}$ isomer)**



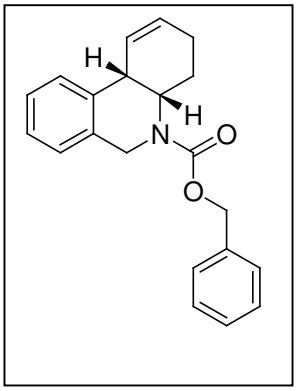

**$R_f$** [hexane:EtOAc, 10:1] = 0.39; **$R_t$** [hexane:EtOAc, 92:8] 18 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3352, 1699 (C=O), 1392, 1367, 1167; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.24-7.16 (4H, m, 4xAr*H*), 5.70-5.66 (1H, m, $CHCH_2CH$=), 5.45-5.37 (1H, m, $NCHCH_2CH$=), 4.68-4.66 (3H, m, $CH_2Ar+NCHCH_2$), 3.32-3.18 (1H, m, $CHCH_2$), 2.86 (1H, dd, *J* 18.0, 4.5, $CH_AH_B$), 2.67-2.54 (1H, m, $CH_AH_B$), 2.28-2.16 (1H, m, $CH_CH_D$), 1.65-1.52 (10H, m, $3xCH_3+CH_CH_D$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 154.8 (C), 136.4 (C), 133.9 (C), 126.6 (CH), 126.4 (CH), 126.1 (CH), 125.4 (CH), 124.8 (CH), 123.7 (CH), 79.6 (C), 50.3 (CH), 44.6 ($CH_2$), 35.5 (CH), 28.5 ($3xCH_3$), 26.2 ($CH_2$); ***m/z*** (EI) 285 ($[M]^+$, 2 %), 231 (32), 175 (100), 130 (22); **HRMS** (EI) Found: $[M]^+$ 285.1726. $C_{18}H_{23}NO_2$ requires 285.1723.

**(4a*SR*,10b*SR*)-2,4a,6,10b-Tetrahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 98b ($\Delta^{3,4}$ isomer)**




**$R_f$** [hexane:EtOAc, 10:1] = 0.44; **$R_t$** [hexane:EtOAc, 92:8] 16 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3359, 1695 (C=O), 1400, 1367; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.37 (1H, d, *J* 7.5, Ar*H*), 7.26-7.13 (2H, m, 2xAr*H*), 7.07 (1H, d, *J* 7.0, Ar*H*), 5.72-5.65 (1H, m, $CH_2CH$=CH), 5.52 (1H, d, *J* 11.0, CH=C*H*CH), 5.08 (1H, br s, NC*H*), 4.86 (1H, d, *J* 17.0, $CH_XH_YAr$), 4.24 (1H, d, *J* 17.0, $CH_XH_YAr$), 3.30 (1H, br s, $CHCH_2$), 2.45-2.37 (1H, m, $CH_ACH_B$), 2.08-1.94 (1H, m, $CH_AH_B$), 1.95-1.81 (2H, m, $CH_2$), 1.50 (9H, s, $3xCH_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 154.8 (C), 135.1 (C), 133.9 (C), 130.8 (CH), 127.6 (CH), 126.5 (2xCH), 125.8 (CH), 125.6 (CH), 79.8 (C), 50.0 (CH), 42.6 ($CH_2$), 34.5 (CH), 28.4 ($3xCH_3$), 25.0 ($CH_2$), 20.2 ($CH_2$); ***m/z*** (EI) 285 ($[M]^+$, 2 %), 229 (77), 228 (100), 184 (32), 175 (48); **HRMS** (EI) Found: $[M]^+$ 285.1720. $C_{18}H_{23}NO_2$ requires 285.1723.

**(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-3H-phenanthridine-5-carboxylic acid benzyl ester 96c ($\Delta^{1,2}$ isomer)**



**$R_f$** [hexane:EtOAc, 10:1] = 0.34; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3030, 1698 (C=O), 1410, 1263; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.29-7.22 (6H, m, 6xAr*H*), 7.19-7.07 (2H, m, 2xAr*H*), 7.01 (1H, d, *J* 6.1, Ar*H*), 6.06-6.02 (1H, m, C*H*=CH), 5.77-5.73 (1H, m, CH=C*H*), 5.12 (2H, s, $CH_2$Ph), 4.72 (1H, d, *J* 16.6, $CH_XH_YAr$), 4.41 (1H, br s, NC*H*CH), 4.36 (1H, d, *J* 16.6, $CH_XH_YAr$), 3.49 (1H, br s, C*H*CH=CH), 2.24-2.09 (1H, m, $CH_AH_B$), 2.07-1.95 (1H, m, $CH_AH_B$), 1.67-1.63 (1H, m, $CH_CH_D$), 1.56-1.48 (1H, m, $CH_CH_D$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.5 (C), 137.6 (C), 136.9 (C), 132.0 (C), 128.4 (2xCH), 128.3 (CH), 127.9 (CH), 127.8 (2xCH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 126.0 (CH), 126.0 (CH), 67.1 ($CH_2$), 50.7 (CH), 43.6 ($CH_2$), 37.2 (CH), 25.1 ($CH_2$), 24.2 ($CH_2$) ; ***m/z*** (FAB, THIOG) 320 ($[M+H]^+$, 24 %), 318 ($[M-H]^+$, 51), 274 (37), 228 (26), 154 (61); **HRMS** (FAB, THIOG) Found: $[M-H]^+$ 318.1483. $C_{21}H_{20}NO_2$ requires 318.1494.

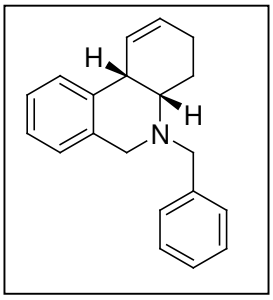
**Diagnostic $^1$H NMR data for 97c ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 5.69-5.65 (1H, m, C*H*=CH), 5.41-5.37 (1H, m, CH=CH), 4.65 (1H, d, *J* 16.6, $CH_XH_YAr$), 4.59 (1H, d, *J* 16.6, $CH_XH_YAr$), 3.20 (1H, br s, C*H*$CH_2$), 2.88-2.81 (1H, m, $CH_AH_B$), 2.63-2.55 (1H, m, $CH_AH_B$).

**Diagnostic $^1$H NMR data for 98c ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 5.75-5.71 (1H, m, C*H*=CH), 5.55 (1H, d, *J* 9.7, CH=C*H*), 4.95 (1H, d, *J* 16.6, $CH_XH_YAr$), 4.33 (1H, d, *J* 16.6, $CH_XH_YAr$), 3.33 (1H, br s, C*H*$CH_2$);

**(4a*SR*,10b*SR*)-5-(Benzyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 96d ($\Delta^{1,2}$ isomer)**




**$R_f$** [hexane:EtOAc, 10:1] = 0.44; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3025, 1642, 1602, 1260; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.35 (2H, d, *J* 7.0, 2xAr*H*), 7.29-7.20 (4H, m, 4xAr*H*), 7.19 (1H, t, *J* 7.6, Ar*H*), 7.10 (1H, t, *J* 7.6, Ar*H*), 6.89 (1H, d, *J* 7.6, Ar*H*), 6.06-6.02 (1H, ddt, *J* 9.8, 4.2, 1.8, CHC*H*=CH), 5.73-5.70 (1H, ddt, *J* 9.8, 5.5, 2.4, CH=C*H*$CH_2$), 3.89 (1H, d, *J* 13.3, C$H_X$$H_Y$Ar), 3.75 (1H, d, *J* 15.6, C$H_P$$H_Q$Ar), 3.66 (1H, d, *J* 13.3, $CH_X$$H_Y$Ar), 3.58 (1H, br s, C*H*CH=CH), 3.54 (1H, d, *J* 15.6, $CH_P$$H_Q$), 3.14 (1H, ddd, *J* 10.6, 5.2, 2.5, NC*H*$CH_2$), 2.21-2.07 (2H, m, =CHC$H_2$), 1.86-1.77 (1H, m, C$H_A$$H_B$), 1.69-1.61 (1H, m, $CH_A$$H_B$); **$^{13}$C NMR** δ (90.0 MHz, $CDCl_3$) 139.0 (C), 137.7 (C), 133.4 (C), 128.8 (CH), 128.7 (2xCH), 128.2 (2xCH), 127.7 (CH), 127.4 (CH), 126.9 (CH), 126.4 (2xCH), 125.2 (CH), 58.4 ($CH_2$), 56.1 (CH), 50.9 ($CH_2$), 37.8 (CH), 24.3 ($CH_2$), 19.4 ($CH_2$); ***m/z*** (FAB, THIOG) 276 ($[M+H]^+$, 76 %), 200 (35), 184 (55), 154 (93), 136 (83); **HRMS** (FAB, THIOG) Found: $[M+H]^+$ 276.1755. $C_{20}H_{22}N$ requires 276.1754. This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

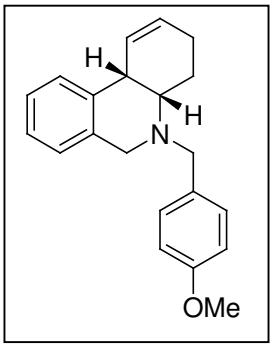
**Diagnostic $^1$H NMR data for 97d ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, $CDCl_3$) 5.70-5.67 (1H, m), 5.58-5.55 (1H, m), 2.74-2.65 (1H, m).

**Diagnostic $^1$H NMR data for 98d ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, $CDCl_3$) 5.96-5.92 (1H, m), 5.89-5.86 (1H, m).

**(4a*SR*,10b*SR*)-5-(4-Methoxy-benzyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 96e ($\Delta^{1,2}$ isomer)**




**$R_f$** [hexane:EtOAc, 10:1] = 0.23; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3024, 1647, 1609, 1511; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.33-7.29 (3H, m, 3xAr*H*), 7.18 (1H, t, *J* 7.3, Ar*H*), 7.10 (1H, t, *J* 7.6, Ar*H*), 6.96 (1H, d, *J* 7.6, Ar*H*), 6.90-6.88 (2H, m, 2xAr*H*), 6.12-6.08 (1H, m, CHC*H*=CH), 5.79-5.76 (1H, m, CH=C*H*$CH_2$), 3.89 (1H, d, *J* 13.0, $CH_XH_YAr$), 3.82 (3H, s, $OCH_3$), 3.80 (1H, d, *J* 16.1, $CH_PH_QAr$), 3.67 (1H, d, *J* 13.0, $CH_XH_YAr$), 3.62 (1H, br s, C*H*CH=), 3.59 (1H, d, *J* 16.1, $CH_PH_Q$), 3.12 (1H, ddd, *J* 10.6, 5.4, 2.6, NC*H*), 2.20-2.00 (2H, m, $CH_2$), 1.90-1.63 (2H, m, $CH_2$); **$^{13}$C NMR** δ (90.0 MHz, $CDCl_3$) 158.6 (C), 137.7 (C), 133.4 (C), 130.9 (C), 129.9 (2xCH), 128.8 (CH), 127.6 (CH), 127.4 (CH), 126.4 (CH), 126.3 (CH), 125.2 (CH), 113.6 (2xCH), 57.7 ($CH_2$), 55.9 (CH), 55.1 ($CH_3$), 50.8 ($CH_2$), 37.8 (CH), 24.4 ($CH_2$), 19.2 ($CH_2$); ***m/z*** (FAB, THIOG) 306 ($[M+H]^+$, 56 %), 305 ($[M]^+$, 58), 304 ($[M-H]^+$, 69), 251 (12.4), 184 (46.1); **HRMS** (FAB, 3-NOBA) Found: $[M]^+$ 305.1779. $C_{21}H_{23}NO$ requires 305.1780. This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

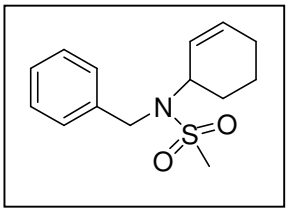
**Diagnostic $^1$H NMR data for 97e ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, $CDCl_3$) 5.68-5.65 (1H, m), 5.56-5.53 (1H, m), 3.98 (1H, d, *J* 13.2), 3.18 (1H, br s), 2.71-2.65 (1H, m).

**Diagnostic $^1$H NMR data for 98e ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, $CDCl_3$) 5.96-5.91 (1H, m), 5.90-5.84 (1H, m), 4.05 (1H, *J* 13.3), 3.11 (1H, br s).

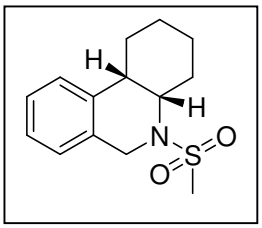
***N*-Benzyl-*N*-cyclohex-2-enyl-methanesulfonamide 99a**



General procedure **B** was followed using *N*-Benzyl-cyclohex-2-enyl amine[176] (590 mg, 3.15 mmol), $CH_2Cl_2$ (15 ml), $Et_3N$ (1.33 ml, 3.47 mmol) and methanesulfonyl chloride (0.73 ml, 9.45 mmol). Flash chromatography (hexane:EtOAc, 10:1–2:1) afforded colourless solid **99a** (300 mg, 63%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.47; **MP** 89 °C ($Et_2O$); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$1334 ($SO_2$), 1143 ($SO_2$); **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.40-7.25 (5H, m, 5xAr*H*), 5.97-5.91 (1H, m, CHNC*H*=CH), 5.57-5.51 (1H, m, CHNCH=C*H*), 4.63-4.53 (1H, m, C*H*N), 4.47 (1H, d, *J* 16.1, C$H_X$H$_Y$Ph), 4.25 (1H, d, *J* 16.1, CH$_X$$H_Y$Ph), 2.79 (3H, s, C$H_3$), 1.98-1.93 (3H, m, C$H_A$H$_B$+C$H_2$), 1.72-1.48 (3H, m, CH$_A$$H_B$+C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 138.4 (C), 132.8 (CH), 128.2 (2xCH), 127.7 (2xCH), 127.5 (CH), 127.1 (CH), 55.5 (CH), 47.2 ($CH_2$), 40.4 ($CH_3$), 28.9 ($CH_2$), 24.2 ($CH_2$), 21.5 ($CH_2$); ***m/z*** (FAB, THIOG) ([2M+H]$^+$, 571, 21.3 %), ([M+H]$^+$ , 266, 70.1), 250 (33.2), 237 (35.6), 214 (49.5); **HRMS** (FAB, THIOG) Found: [M+H]$^+$, 266.1218. $C_{14}H_{19}NO_2S$ requires 266.1215.

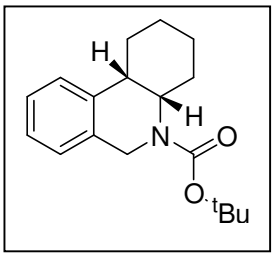
**(4a*SR*,10b*SR*)-5-Methanesulfonyl-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine 110**



To a solution of phenanthridines **96a**-**98a** (316 mg, 1.18 mmol) in ethanol (10 ml) was added EtOAc (1 ml) and Pd/C (35 mg, 10% by weight). The reaction was stirred vigorously and exposed to an atmosphere of hydrogen for 12 h. The reaction was filtered through celite and concentrated under reduced pressure to afford phenanthridine **110** as a colourless solid (190 mg, 60%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.33; **MP** 103 $^oC$ (EtOH); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3029, 1684, 1325 ($SO_2$), 1153 ($SO_2$); **$^1H$ NMR** δ (360 MHz, $CDCl_3$) 7.39 (1H, d, *J* 7.7, Ar*H*), 7.25 (1H, t, *J* 6.0, Ar*H*), 7.21 (1H, t, *J* 6.1, Ar*H*), 7.11 (1H, d, *J* 6.7, Ar*H*), 4.64 (1H, d, *J* 16.3, C$H_X$H$_Y$Ar), 4.42 (1H, d, *J* 16.3, CH$_X$$H_Y$Ar), 4.14-4.09 (1H, m, C*H*N), 3.26 (1H, br s, C*H*CHN), 2.89 (3H, s, C$H_3$), 2.55-2.49 (1H, m, C$H_A$H$_B$), 1.83-1.65 (3H, m, C$H_2$+CH$_A$$H_B$), 1.48-1.42 (3H, m, C$H_2$+C$H_C$H$_D$), 1.26-1.15 (1H, m, CH$_C$$H_D$); **$^{13}C$ NMR** δ (90.6 MHz, $CDCl_3$) 134.7 (C), 131.8 (C), 127.1 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 54.0 (CH), 43.6 ($CH_2$), 38.8 ($CH_3$), 37.1 (CH), 27.6 ($CH_2$), 26.3 ($CH_2$), 25.0 ($CH_2$), 19.6 ($CH_2$); ***m/z*** (FAB, THIOG) 529 $(2M+H)^+$, 10 %), 266 $([M+H]^+$, 83), 264 (94), 262 (29), 234 (17), 222 (18); **HRMS** (FAB, THIOG) Found: $[M+H]^+$ 266.1214. $C_{14}H_{20}NO_2S$ requires 266.1215.

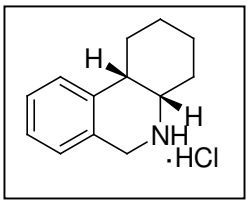
**(4a*SR*,10b*SR*)-2,3,4,4a,6,10b-Hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 111**




To a solution of phenanthridines **96b**-**98b** (200 mg, 0.71 mmol) in methanol (20 ml) was added Pd/C (20 mg, 10% by weight). The reaction was stirred vigorously and exposed to an atmosphere of hydrogen for 16 h. The reaction was filtered through celite, concentrated under reduced pressure and purified by flash chromatography ($CH_2Cl_2$:EtOAc, 1:1) to afford phenanthridine **111** as a colourless oil (179 mg, 88%).

**$R_f$** [hexane:EtOAc, 10:1] = 0.47; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2927, 1693 (C=O), 1366, 1174; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.37 (1H, d, *J* 7.6, Ar*H*), 7.28-7.14 (2H, m, 2xAr*H*), 7.13 (1H, d, *J* 6.5, Ar*H*), 4.72 (1H, d, *J* 17.1, C$H_X$$H_Y$Ar), 4.39 (1H, d, *J* 17.1, C$H_X$$H_Y$Ar), 4.32-4.29 (1H, m, NC*H*CH), 3.20 (1H, br s, NCHC*H*), 2.57-2.52 (1H, m, C$H_A$$H_B$), 1.84-1.72 (1H, m, C$H_A$$H_B$), 1.72-1.60 (2H, m, C$H_2$), 1.60-1.20 (13H, m, 3 x C$H_3$+C$H_2$C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.8 (C), 135.7 (C), 133.8 (C), 126.6 (CH), 126.3 (CH), 125.8 (CH), 125.7 (CH), 79.5 (C), 52.4 (CH), 43.8 ($CH_2$), 36.8 (CH), 28.5 (3x$CH_3$), 27.4 ($CH_2$), 26.5 ($CH_2$), 25.5 ($CH_2$), 19.9 ($CH_2$); ***m/z*** (FAB, THIOG) 286 ($[M-H]^+$, 31 %), 230 (75), 186 (55), 184 (18), 156 (12), 130 (17), 57 (100); **HRMS** (FAB, THIOG) Found: $[M-H]^+$ 286.1812. $C_{18}H_{24}NO_2$ requires 286.1807.

**(4a*SR*,10b*SR*)-1,2,3,4,4a,5,6,10b-Octahydro-phenanthridinium; chloride 112**[87]



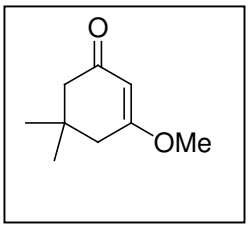

To a solution of Boc-protected amine **111** (154 mg, 0.54 mmol) in $CH_2Cl_2$ (10 ml) was added Trifluoroacetic acid (15.0 ml). After 10 minutes no starting material remained by TLC so the solution was adjusted to pH 9 using KOH pellets and extracted with $CH_2Cl_2$ (3 x 15 ml). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2$ (1 ml), HCl added (1 ml, 1.0 M in $Et_2O$, 1 mmol) and the resultant suspension filtered to afford octahydrophenanthridinium chloride **112** as a pale yellow solid (106 mg, 88%).

**MP** 173 °C ($Et_2O$); $\upsilon_{max}$ ($CHCl_3$)/$cm^{-1}$ 3421 (NH); **$^1$H NMR** δ (360 MHz, $CD_3OD$) 9.19 (1H, brs, N*H*), 7.97 (1H, d, *J* 7.5, Ar*H*), 7.91 (1H, t, *J* 7.6, Ar*H*), 7.63 (1H, d, *J* 7.6, Ar*H*), 7.59 (1H, d, *J* 7.9, Ar*H*), 4.90 (2H, s, C$H_2$Ar), 4.33 (1H, brs, NC*H*CH), 3.30 (1H, m, NCHC*H*), 2.30-2.15 (1H, m, C$H_A$H$_B$), 2.08-1.90 (1H, m, CH$_A$$H_B$), 1.89-1.70 (2H, m, C$H_2$), 1.56 (2H, brs, C$H_2$); **$^{13}$C NMR** δ (90.0 MHz, $CD_3OD$) 142.9 (C), 138.0 (CH), 133.6 (CH), 127.7 (CH), 127.3 (CH), 122.8 (C), 53.4 (CH), 48.0 ($CH_2$), 36.0 (CH), 27.7 ($CH_2$), 25.9 ($CH_2$), 22.3 ($CH_2$), 20.0 ($CH_2$); ***m/z*** (FAB, THIOG) 188 ([M+H]$^+$, 100 %), 156 (54), 144 (57), 130 (68); **HRMS** (FAB, THIOG) Found: [M+H]$^+$ 188.1436. $C_{13}H_{18}N$ requires 188.1439.

**Free Amine**: **$R_f$** [EtOAc] = 0.29; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.02 (1H, d, *J* 6.5, Ar*H*), 7.16-7.08 (3H, m, 3xAr*H*), 4.16 (1H, d, *J* 16.2, C$H_X$H$_Y$), 4.10 (1H, d, *J* 16.2 CH$_X$$H_Y$), 3.16 (1H, d, *J* 3.3, NC*H*CH), 2.65-2.62 (1H, m, NCHC*H*), 2.16 (1H, br s, N*H*), 1.97-1.91 (1H, d, *J* 23.1, C$H_A$H$_B$), 1.86-1.69 (3H, m, CH$_A$$H_B$+C$H_2$), 1.65-1.36 (4H, m, $CH_2$+$CH_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 140.7 (C), 134.6 (C), 128.7 (CH), 126.9 (CH), 125.8 (CH), 125.7 (CH), 52.0 (CH), 48.7 ($CH_2$), 39.0 (CH), 31.7 ($CH_2$), 31.2 ($CH_2$), 25.8 ($CH_2$), 20.4 ($CH_2$).

$^1$H and $^{13}$C NMR data in good agreement with the literature.[87]

**3-Methoxy-5,5-dimethyl-cyclohex-2-enone 117**[177]

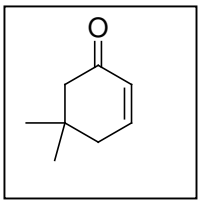



To a solution of dimedone (4.90 g, 34.9 mmol) in MeOH (100 ml) was added cerium(IV) ammonium nitrate (1.91 g, 3.49 mmol) and the reaction stirred for 16 h at r.t. The reaction was concentrated under reduced pressure and the organics taken up in $Et_2O$ (200 ml) and washed with NaCl (3 x 100 ml, sat. aq.). The organics were dried ($MgSO_4$), concentrated under reduced pressure, and purified using flash chromatography (hexane:EtOAc, 10:1-2:1) to afford enol ether **117** as a pale yellow oil (3.90 g, 73%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.15; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1656 (C=O), 1608, 1376, 1226, 1155; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 5.35 (1H, s, C=C*H*), 3.67 (3H, s, OC$H_3$), 2.25 (2H, s, C$H_2$), 2.19 (2H, s, C$H_2$), 1.04 (6H, s, 2xC$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 199.4 (C), 176.9 (C), 100.9 (CH), 55.5 ($CH_3$), 50.5 ($CH_2$), 42.5 ($CH_2$), 32.3 (C), 28.1 (2x$CH_3$); ***m/z*** (FAB, THIOG) 155 ($[M+H]^+$, 100 %), 139 (28), 124 (12), 110 (16); **HRMS** (FAB, THIOG) Found: $[M+H]^+$ 155.1073. $C_9H_{15}O_2$ requires 155.1072.

$^1$H and $^{13}$C NMR data in good agreement with the literature.[177]

**5,5-Dimethyl-cyclohex-2-enone 118**[89]

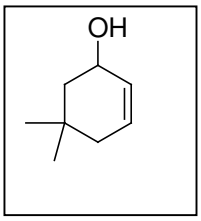


To a solution of enol ether **117** (900 mg, 5.84 mmol) in $Et_2O$ (12 ml) at 0 °C was added $LiAlH_4$ (255 mg, 6.72 mmol) portionwise. The reaction was warmed to r.t. and stirred for 1 h. The $LiAlH_4$ was quenched by adding $Na_2SO_4.5H_2O$ portionwise, then the reaction was filtered and the filtrate concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2$ (10 ml) and stirred with silica (cat.) for 3 h to afford enone **118** as a colourless oil (661 mg, 91%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.55; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1678 (C=O), 1609, 1389, 1161; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 6.75 (1H, dt, *J* 10.1, 4.2, C*H*=CH), 5.88 (1H, dt, *J* 10.1, 2.1, CH=C*H*), 2.14 (2H, s, C$H_2$), 2.13 (2H, dd, *J* 4.2, 2.1, C$H_2$CH=), 0.89 (6H, s, 2xC$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 199.8 (C), 148.2 (CH), 128.9 (CH), 51.6 ($CH_2$), 39.8 ($CH_2$), 33.7 (C), 28.2 (2x$CH_3$); ***m/z*** (FAB, THIOG) 125 ($[M+H]^+$, 96 %), 122 (43), 120 (35) 116 (33), 111 (73), 109 (92); **HRMS** (FAB, THIOG) Found: $[M+H]^+$ 125.0968. $C_8H_{13}O$ requires 125.0966.

$^1$H and $^{13}$C NMR data in good agreement with the literature.[89]

**5,5-Dimethyl-cyclohex-2-enol 119**[90]

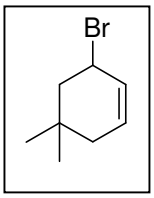



To a solution of enone **118** (661 mg, 5.32 mmol) in $Et_2O$ (12 ml) at 0 °C was added portionwise $LiAlH_4$ (201 mg, 5.32 mmol). The reaction was stirred for at 0 °C for 40 mins then quenched by the addition of $Na_2SO_4.5H_2O$ portionwise. The reaction was filtered and the filtrate vigorously stirred with potassium sodium tartate (50 ml, sat. aq.) for 1 h. The organic phase was separated and the aqueous phase washed with $Et_2O$ (3 x 40 ml). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford alcohol **119** as a colourless oil (525 mg, 72%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.37; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3336 (OH), 2952, 1650, 1454, 1089; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 5.71 (2H, s, C*H*=C*H*), 4.29-4.22 (1H, m, C*H*OH), 1.88-1.57 (3H, m, $CH_2$+$CH_AH_B$), 1.31 (1H, dd, *J* 12.3, 8.7, $CH_AH_B$), 1.00 (3H, s, $CH_3$), 0.92 (3H, s, $CH_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 129.1 (CH), 128.0 (CH), 66.2 (CH), 45.3 ($CH_2$), 38.9 ($CH_2$), 31.2 ($CH_3$), 30.7 (C), 26.0 ($CH_3$); ***m/z*** (FAB, THIOG) 149 ($[M+Na]^+$, 33 %), 127 ($[M+H]^+$, 5), 125 ($[M-H]^+$, 12), 124 (18), 111 (53); **HRMS** (FAB, THIOG) Found: $[M-H]^+$ 125.0968. $C_8H_{13}O$ requires 125.0966.

$^1$H and $^{13}$C NMR data in good agreement with the literature.[90]

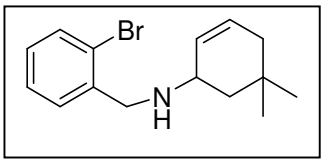
**3-Bromo-5,5-Dimethyl-cyclohex-2-ene 120**




To a stirred solution of alcohol **119** (2.00 g, 15.8 mmol) and $CBr_4$ (11.1 g, 33.3 mmol) in $Et_2O$ (75 ml) at 0 $^oC$ was added $PPh_3$ (8.00 g, 33.3 mmol). The reaction was warmed to r.t. and stirred for 2 h. The reaction was filtered and the filtrate concentrated under reduced pressure to afford a colourless solid and a yellow oil. These were washed with pentane (2 x 100 ml) and the combined washings dried ($MgSO_4$) and concentrated under reduced pressure to afford bromide **120** as a pale yellow oil (2.00 g, 67%). This material was found to be unstable to flash chromatography and thus was used without further purification.

**$R_f$** [hexane:EtOAc, 3:1] = 0.46; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1437, 1120, 723, 694; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 5.90-5.84 (1H, m, C*H*=CH), 5.75-5.71 (1H, m, CH=C*H*), 4.79-4.77 (1H, m, C*H*Br), 2.14-1.88 (3H, m, $CH_AH_B$+$CH_2$), 1.80-1.70 (1H, m, $CH_AH_B$), 1.02 (3H, s, $CH_3$), 0.96 (3H, s, $CH_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 129.0 (CH), 128.2 (CH), 47.5 (CH), 46.7 ($CH_2$), 38.1 ($CH_2$), 31.9 (C), 30.7 ($CH_3$), 25.4 ($CH_3$).

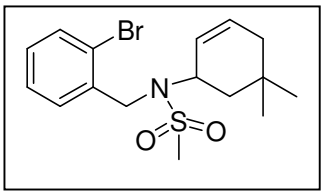
***N*-(2-Bromo-benzyl)-5,5-dimethylcyclohex-2-enyl-amine 121**




To a suspension of 2-bromobenzylamine hydrochloride (412 mg, 1.85 mmol) in MeCN (20 ml) was added $^{i}Pr_2NEt$ (1.30 ml, 7.40 mmol) and the reaction stirred for 10 mins. Cyclohexenyl bromide **120** (700 µl, 3.70 mmol) was added dropwise and the reaction stirred at r.t. for 16 h. The reaction was concentrated under reduced pressure and the residue taken up in $CH_2Cl_2$ (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford amine **121** as a brown oil (340 mg, 63%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.37; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3307 (NH), 1776, 1651, 1466; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.53 (1H, dd, *J* 7.9, 1.2, Ar*H*), 7.46 (1H, dd, *J* 6.1, 1.6, Ar*H*), 7.28 (1H, t, *J* 7.4, 6.1, Ar*H*), 7.11 (1H, td, *J* 7.8, 1.6, Ar*H*), 5.76-5.70 (2H, m, C*H*=C*H*), 3.92 (2H, s, C$H_2$Ar), 3.31-3.24 (1H, m, C*H*N), 1.92 (1H, dd, *J* 17.8, 3.4, C$H_A$H$_B$), 1.79-1.71 (2H, m, CH$_A$$H_{B+}$C*H*CH$_D$), 1.23 (1H, dd, CH$_C$$H_D$), 1.00 (3H, s, C$H_3$), 0.92 (3H, s, C$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 139.6 (C), 132.5 (CH), 130.0 (CH), 128.4 (CH), 128.3 (CH), 127.3 (CH), 127.2 (CH), 123.7 (C), 52.0 (CH), 50.7 ($CH_2$), 43.2 ($CH_2$), 39.0 ($CH_2$), 31.8 ($CH_3$), 30.2 (C), 25.4 ($CH_3$); ***m/z*** (FAB, THIOG) 296 ([$^{81Br}$M+H]$^+$, 96 %), 294 ([$^{79Br}$M+H]$^+$, 100), 239 (25), 188 (33), 186 (51), 171 (42), 169 (48) ; **HRMS** (FAB, THIOG) Found: [$^{81Br}$M+H]$^+$ 296.0845. $C_{15}H_{21}N^{81}Br$ requires 296.0837. Found: [$^{79Br}$M+H]$^+$, 294.0848. $C_{15}H_{21}N^{79}Br$ requires 294.0857.

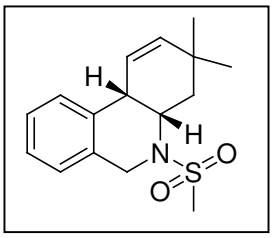
**_N_-(2-Bromo-benzyl)-_N_-5,5-dimethylcyclohex-2-enyl-methanesulfonamide 115**




General procedure **B** was followed using amine hydrochloride **121** (180 µl, 0.62mmol), $CH_2Cl_2$ (5 ml), $Et_3N$ (262 µl, 1.87 mmol) and methanesulfonyl chloride (214 µl, 1.87 mmol). Flash chromatography (hexane:EtOAc, 10:1–5:1) afforded sulfonamide **115** as a colourless oil (150 mg, 65%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.77; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1335 ($SO_2$), 1159 ($SO_2$), 913, 745; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.66 (1H, d, *J* 7.0, Ar*H*), 7.50 (1H, dd, *J* 8.0, 1.2, Ar*H*), 7.32 (1H, td, *J* 7.6, 0.7, Ar*H*), 7.11 (1H, *J* 7.6, 1.8, Ar*H*), 5.89-5.83 (1H, dddd, *J* 10.3, 5.2, 2.7, 2.5, C*H*=CH), 5.49 (1H, dd, *J* 10.3, 1.3, CH=C*H*), 4.63-4.47 (1H, m, C*H*N), 4.45 (1H, d, *J* 17.6, $CH_XH_Y$), 4.31 (1H, d, *J* 17.6, $CH_XH_Y$), 2.98 (3H, s, $CH_3$), 1.92-1.83 (1H, m, $CH_AH_B$), 1.75-1.68 (1H, m, $CH_AH_B$), 1.68-1.60 (1H, m, $CH_CH_D$), 1.30-1.25 (1H, m, $CH_CH_D$), 0.95 (3H, s, $CH_3$), 0.91 (3H, s, $CH_3$) ; **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 137.7 (C), 132.1 (2xCH), 129.3 (CH), 128.5 (CH), 127.4 (CH), 125.1 (CH), 122.0 (C), 54.9 (CH), 47.7 ($CH_2$), 40.8 ($CH_2$), 39.5 ($CH_3$), 38.2 ($CH_2$), 31.7 ($CH_3$), 31.0 (C), 24.8 ($CH_3$); ***m/z*** (FAB, THIOG) 374 ([$^{81Br}$M+H]$^+$, 80 %), 372 ([$^{79Br}$M+H]$^+$, 93), 294 (49), 292 (53), 264 (23), 262 (12), 171 (100), 169 (100); **HRMS** (FAB, THIOG) Found: [$^{81Br}$M+H]$^+$, 374.0612. $C_{16}H_{23}O_2NS^{81}Br$ requires 374.0612. Found: [$^{79Br}$M+H]$^+$, 372.0628. $C_{16}H_{23}O_2NS^{79}Br$ requires 372.0633.

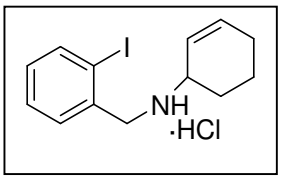
**(4a*SR*,10b*SR*)-3,3-dimethyl-5-Methanesulfonyl-4,4a,5,6,10b-tetrahydro-phenanthridine 114**




General procedure **C** was employed using sulfonamide **115** (40 mg, 0.11 mmol), palladacycle **100** (5.0 mg, 5.4 μmol) and $Ag_2CO_3$ (30 mg, 0.11 mmol) in DMF (3 ml). After 2 h at 140 $^oC$, work up and column chromatography (hexane:EtOAc, 10:1-5:1) afforded phenanthridine **114** as a colourless solid (31 mg, 99%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.48; **MP** 104 $^oC$ (hexane); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2957, 1332 ($SO_2$), 1153 ($SO_2$); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.32 (1H, d, *J* 7.5, Ar*H*), 7.24 (1H, t, *J* 7.3, Ar*H*), 7.20 (1H, t, *J* 7.9, Ar*H*), 7.10 (1H, d, *J* 7.3, Ar*H*), 6.03 (1H, dd, *J* 10.0, 5.6, C*H*=CH), 5.59 (1H, d, *J* 10.0, CH=C*H*), 4.60 (1H, d, *J* 16.2, $CH_XH_Y$), 4.43 (1H, d, *J* 16.2, $CH_XH_Y$), 4.41 (1H, dd, *J* 15.5, 6.2, C*H*N), 3.59 (1H, tr, *J* 5.6, C*H*CH=CH), 2.87 (3H, s, $CH_3$), 1.64-1.60 (2H, m, $CH_2$), 1.15 (3H, s, $CH_3$), 0.94 (3H, s, $CH_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 138.7 (CH), 136.3 (C), 130.3 (C), 127.9 (CH, $C_{10}$), 127.3 (CH), 126.1 (CH), 126.0 (CH, $C_7$), 123.7 (CH, $C_1$), 49.8 (CH, $C_{4a}$), 43.3 ($CH_2$, $C_6$), 39.0 ($CH_3$, $SO_2Me$), 38.2 ($CH_2$, $C_4$), 36.6 (CH), 34.0 (C, $C_3$), 30.3 ($CH_3$), 28.3 ($CH_3$); ***m/z*** (FAB, THIOG) 292 ($[M+H]^+$, 100 %), 291 ($[M]^+$, 82), 213 (44), 197 (40), 165 (12), 130 (15), 94 (89); **HRMS** (FAB, THIOG) Found: $[M+H]^+$ 292.1371. $C_{16}H_{22}NO_2S$ requires 292.1371.

***N*-(2-Iodo-benzyl)-cyclohex-2-enyl-amine hydrochloride 129**

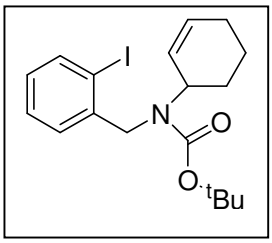



General procedure **A** was followed using 2-iodobenzylamine hydrochloride (200 mg, 0.742 mmol), MeCN (5 ml) at 0 °C $^{i}Pr_2NEt$ (517 µl, 2.97 mmol), 3-bromocyclohexene (86.0 µl, 0.742 mmol) and HCl (2 ml, 1 M in $Et_2O$, 2.00 mmol) to afford amine hydrochloride **129** as a colourless solid (287 mg, 100%).

**MP** 241 °C; **$^1$H NMR** δ (360 MHz, $CD_3OD$) 8.05 (1H, dd, *J* 8.0, 1.1, Ar*H*), 7.65 (1H, dd, *J* 7.7, 1.6, Ar*H*), 7.55 (1H, td, *J* 7.5, 1.1, Ar*H*), 7.23 (1H, td, *J* 7.9, 1.6, Ar*H*), 6.29 (1H, m, C*H*=H), 5.91 (1H, dd, *J* 9.6, 1.4, CH=C*H*), 4.45 (2H, s, C$H_2$Ar), 4.10-4.04 (1H, m, C*H*N), 2.29-2.18 (3H, m, C$H_2$+C$H_A$H$_B$), 1.99-1.91 (2H, m, C$H_2$), 1.83-1.70 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (90.6 MHz, $CD_3OD$) 141.9 (C), 136.8 (CH), 135.9 (C), 132.6 (CH), 132.5 (CH), 130.4 (CH), 122.7 (CH), 101.9 (C), 55.8 (CH), 54.0 ($CH_2$), 26.6 ($CH_2$), 25.6 ($CH_2$), 20.6 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 314 ($[M+H]^+$, 99 %), 234 (51), 217 (53), 167 (39), 154 (63), 149 (100), 130 (92) ; **HRMS** (FAB, 3-NOBA) Found: $[M+H]^+$ 314.0409. $C_{13}H_{17}NI$ requires 314.0406.

**Free Amine: $R_f$** [hexane:EtOAc, 3:1] = 0.60; **$\upsilon_{max}$** ($CH_2Cl_2$)/cm$^{-1}$ 3361 (NH), 1562, 1437, 1011, 748.

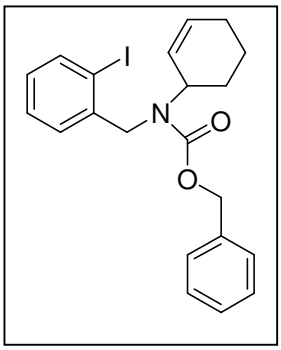
**(2-Iodo-benzyl)-cyclohex-2-enyl-carbamic acid *tert*-butyl ester 124b**




To a suspension of amine hydrochloride **129** (120 mg, 0.34 mmol) in $CH_2Cl_2$ (5 ml) was added $Et_3N$ (72 µl, 0.52 mmol). After 10 mins, the reaction was cooled to 0 $^oC$, $Boc_2O$ (112 mg, 0.52 mmol) in $CH_2Cl_2$ (1 ml) was added and the reaction was stirred for a further 10 mins. The reaction was warmed to r.t. and stirred for 16 h. The reaction was diluted with $CH_2Cl_2$ (10 ml), extracted with NaCl (3 x 10 ml, sat. aq.), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane:EtOAc, 100:1) afforded Boc-protected amine **124b** as a colourless oil (60 mg, 49%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.82; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2930, 1694 (C=O), 1167; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.80 (1H, d, *J* 7.9, Ar*H*), 7.31 (1H, tr, *J* 7.3, Ar*H*), 7.22 (1H, d, *J* 7.6, Ar*H*), 6.92 (1H, t, *J* 7.3, Ar*H*), 5.83 (1H, br s, C*H*=CH), 5.48 (1H, d, *J* 10.0, CH=C*H*), 4.88 (1H, br s, NC*H*), 4.28 (2H, br s, C$H_2$Ar), 2.10-1.81 (3H, m, C$H_2$+C$H_A$H$_B$), 1.81-1.70 (1H, m, CH$_A$$H_B$), 1.55-1.46 (2H, m, C$H_2$), 1.35 (9H, s, 3C$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.7 (C), 140.9 (C), 139.0 (2xCH), 128.1 (2xCH), 127.9 (CH), 127.1 (CH), 97.2 (C), 79.8 (C), 53.2 (CH), 52.9 ($CH_2$), 28.2 (3x$CH_3$), 24.5 (2x$CH_2$), 21.3 ($CH_2$); ***m/z*** (FAB, THIOG) 414 ([M+H]$^+$, 20 %), 359 (100), 232 (22), 217 (41); **HRMS** (FAB, THIOG) Found: [M+H]$^+$ 414.0929. $C_{18}H_{25}NO_2I$ requires 414.0932.

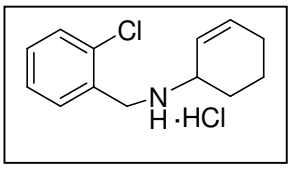
**(2-Iodo-benzyl)-cyclohex-2-enyl-carbamic acid benzyl ester 124c**



To a suspension of NaH (15 mg, 60% dispersion in mineral oil, 0.37 mmol) in DMF (4 ml) at 0 $^{o}$C was added amine hydrochloride **129** (58.0 mg, 0.17 mmol) in DMF (1 ml). The solution was stirred for 30 mins then benzyl chloroformate (31 µl, 0.22 mmol) was added dropwise and the reaction was warmed to r.t. and stirred for 16 h. The reaction was diluted with $Et_2O$ (10 ml), extracted with NaCl (3 x 10 ml, sat. aq.), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Flash chromatography (hexane:EtOAc, 100:3) afforded Cbz protected amide **124c** as a colourless oil (61 mg, 82%).

**$R_f$** [hexane:EtOAc, 10:1] = 0.78; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 1699 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.80 (1H, d, *J* 7.9, 1.5, Ar*H*), 7.40 – 7.21 (7H, m, 7xAr*H*), 7.18 (1H, td, *J* 7.6, 1.5, ArH), 5.87-5.80 (1H, m, C*H*=CH), 5.47 (1H, d, *J* 10.2, CH=C*H*), 5.15 (2H, br s, OC$H_2$Ar), 4.90 (1H, br s, C*H*N), 4.40 (1H, d, *J* 16.9, C$H_X$H$_Y$Ar), 4.33 (1H, d, *J* 16.9, CH$_X$$H_Y$Ar), 2.10-1.85 (3H, m, C$H_2$+C$H_A$H$_B$), 1.80-1.70 (1H, m, CH$_A$$H_B$), 1.70-1.42 (2H, m, C$H_2$) ; **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 156.5 (C), 141.1 (C), 139.1 (2xCH), 131.8 (C), 129.9 (C), 128.2 (3xCH), 128.0 (CH), 127.7 (3xCH), 127.6 (CH), 127.2 (CH), 67.1 ($CH_2$), 53.8 (CH), 45.9 ($CH_2$), 28.1 ($CH_2$), 24.5 ($CH_2$), 21.2 ($CH_2$); ***m/z*** (FAB, THIOG) 448 ([M+H]$^+$, 14 %), 217 (13), 171 (4), 94 (100); **HRMS** (FAB, 3-NOBA) Found [M+H]$^+$ 448.0775. $C_{21}H_{23}O_2IN$ requires 448.0774.

**_N_-(2-Chloro-benzyl)-cyclohex-2-enyl-amine hydrochloride 132**

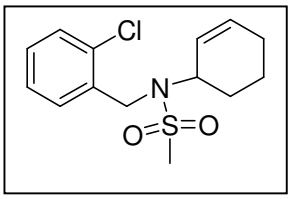



General procedure **A** was followed using 2-chlorobenzylamine (1.00 g, 8.28 mmol), MeCN (20 ml) $^{i}Pr_2NEt$ (4.20 ml, 24.9 mmol), 3-bromocyclohexene (952 µl, 8.28 mmol) and HCl (10 ml, 1 M in $Et_2O$, 10 mmol) to afford amine hydrochloride **132** as a colourless solid (1.20 g, 66%).

**MP** 161 $^{o}$C ($Et_2O$); **$^{1}$H NMR** δ (250 MHz, $CD_3OD$) 7.72-7.69 (1H, m, Ar*H*), 7.62-7.47 (3H, m, 3xAr*H*), 6.28-6.23 (1H, m, C*H*=CH), 5.90 (1H, dd, *J* 10.3, 1.5, CH=C*H*), 4.45 (2H, s, C$H_2$Ar), 4.25-4.22 (1H, br s, C*H*N), 2.26-2.17 (3H, m, C$H_2$+C$H_A$H$_B$), 1.96-1.72 (3H, m, C$H_2$+CH$_A$$H_B$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 136.9 (CH), 136.0 (C), 133.4 (CH), 132.6 (CH), 131.2 (CH), 130.8 (C), 129.0 (CH), 122.4 (CH), 55.8 (CH), 46.6 ($CH_2$), 26.4 ($CH_2$), 25.5 ($CH_2$), 20.5 ($CH_2$); ***m/z*** (FAB, THIOG) 224 ([$^{37Cl}$M+H]$^{+}$, 39 %), 222 ([$^{35Cl}$M+H]$^{+}$, 100), 144 (11), 142 (34), 127 (16), 125 (47) ; **HRMS** (FAB, THIOG) Found: [$^{37Cl}$M+H]$^{+}$, 224.1026. $C_{13}H_{17}N^{37}Cl$ requires 224.1020. Found: [$^{35Cl}$M+H]$^{+}$ 222.1057. $C_{13}H_{17}N^{35}Cl$ requires 222.1050.

**Free amine: $R_f$** [hexane:EtOAc, 3:1] = 0.33; **$\upsilon_{max}$** (MeOH/$CH_2Cl_2$)/cm$^{-1}$ 2937, 2707, 1573, 1445, 762.

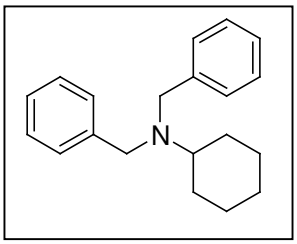
***N*-(2-Chloro-benzyl)-*N*-cyclohex-2-enyl-methanesulfonamide 130a**




General procedure **B** was followed using amine hydrochloride **132** (1.10 g, 4.96 mmol), $CH_2Cl_2$ (30 ml), $Et_3N$ (2.10 ml, 14.9 mmol) and methanesulfonyl chloride (1.15 ml, 14.9 mmol). Flash chromatography (hexane:EtOAc, 10:1-3:1) afforded sulfonamide **130a** as a colourless solid (890 mg, 60%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.59; **MP** 89 $^oC$ ($Et_2O$); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2932, 1333 ($SO_2$), 1145 ($SO_2$); **$^1H$ NMR** δ (250 MHz, $CDCl_3$) 7.68 (1H, dt, *J* 7.2, 1.7, Ar*H*), 7.33-7.19 (3H, m, 3xAr*H*), 5.99-5.93 (1H, m, C*H*=CH), 5.51 (1H, dt, *J* 10.1, 1.6, CH=C*H*), 4.66-4.59 (1H, m, NC*H*), 4.50 (1H, d, *J* 17.5, $CH_XH_YAr$), 4.38 (1H, d, *J* 17.5, $CH_XH_YAr$), 2.96 (3H, s, $CH_3$), 2.00-1.93 (3H, m, $CH_AH_B$+$CH_2$), 1.80-1.33 (3H, m, $CH_AH_B$+$CH_2$); **$^{13}C$ NMR** δ (62.9 MHz, $CDCl_3$) 137.0 (C), 133.7 (CH), 132.5 (C), 129.1 (CH), 128.9 (CH), 128.1 (CH), 126.8 (CH), 126.6 (CH), 55.6 (CH), 44.9 ($CH_2$), 39.4 ($CH_3$), 28.7 ($CH_2$), 24.2 ($CH_2$), 21.4 ($CH_2$); ***m/z*** (FAB, THIOG) 302 ($[^{37Cl}M+H]^+$, 5 %), 300 ($[^{35Cl}M+H]^+$), 220 (17), 127 (34), 125 (100), 109 (12); **HRMS** (FAB, THIOG) Found: $[^{37Cl}M+H]^+$, 302.0805. $C_{14}H_{19}NO_2S^{37}Cl$ requires 302.0800. Found: $[^{35Cl}M+H]^+$, 300.0836. $C_{14}H_{19}NO_2S^{35}Cl$ requires 300.0825.

**Dibenzylcyclohexylamine 133**[100]



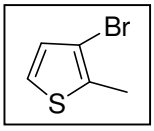
To a suspension of amine **135**[178] (4.62 g, 24.4 mmol) in DMF (100 ml) at 0 °C, was added NaH (2.14 g, 60% dispersion in mineral oil, 54.0 mmol) and the reaction stirred for 30 mins. Benzyl bromide (3.77 ml, 3.77 mmol) was added dropwise and the reaction warmed to r.t and stirred for 16 h. $Et_2O$ (100 ml) was added and the organics washed with NaCl (3 x 100 ml, sat. aq.), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 25:1). The resultant solid was recrystallised from EtOH (10 ml) to afford dibenzylamine **133** as a colourless solid (4.52 g, 61%).

**$R_f$** [hexane:EtOAc, 10:1] = 0.87; **MP** 63 °C (lit 62 °C)[100]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2927, 2852, 2796, 1493, 1452; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.41 (4H, d, *J* 6.9, 4xAr*H*), 7.31 (4H, t, *J* 7.3, 4xAr*H*), 7.23 (2H, t, *J* 7.3, 2xAr*H*), 3.67 (4H, s, 2xC$H_2$Ar), 2.51 (1H, tt, *J* 11.6, 3.4, NC*H*), 1.93 (2H, br d, *J* 12.6, C$H_2$), 1.81-1.78 (2H, m, C$H_2$), 1.64-1.62 (1H, m, C$H_A$H$_B$), 1.42-1.29 (2H, m, C$H_2$), 1.23-1.06 (3H, m, C$H_2$+CH$_A$$H_B$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 141.2 (2xC), 128.2 (4xCH), 127.9 (4xCH), 126.3 (2xCH), 57.6 (CH), 53.7 (2x$CH_2$), 28.5 (2x$CH_2$), 26.4 ($CH_2$), 26.1 (2x$CH_2$); ***m/z*** (EI) 279 ([M]$^+$, 10 %), 236 (18), 181 (7), 138 (11); **HRMS** (EI) Found: [M]$^+$ 279.1979. $C_{20}H_{25}N$ requires 279.1982.

$^1$H Spectroscopic data in good agreement with the literature.[179]

## 6.3 Experimental for Chapter three

### 3-Bromo-2-methyl-thiophene 153[180]

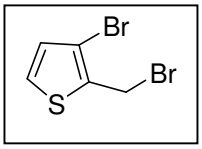



To a solution of diisopropylamine (6.00 ml, 42.6 mmol) in THF (20 ml) at 0 °C was added $^{n}$BuLi (26.6 ml, 42.6 mmol, 1.6 M in hexanes). After addition was complete the reaction temperature was maintained at 0 °C for 30 mins. The flask was cooled to –78 °C, 3-bromothiophene (4.00 ml, 42.6 mmol) was added dropwise and the reaction warmed to 0 °C and stirred for 30 mins. The reaction was cooled again to –78 °C and methyl iodide (2.68 ml, 42.6 mmol) was added. After 30 mins the reaction was warmed to r.t. and stirred for 1 h. The reaction was diluted with $Et_2O$ (100 ml) and washed with $H_2O$ (3 x 50 ml). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford methyl thiophene **153** as a grey oil (7.2 g, 99%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.80; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3110, 2919, 2856, 1527, 1439, 1341; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.08 (1H, d, *J* 5.4, Het*H*), 6.91 (1H, d, *J* 5.4, Het*H*), 2.43 (3H, s, C*H*$_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 134.0 (C), 129.7 (CH), 127.4 (CH), 109.2 (C), 14.4 ($CH_3$).

$^1$H and $^{13}$C NMR spectroscopic data in good agreement with the literature.[180]

### 3-Bromo-2-bromomethyl-thiophene 154[104]

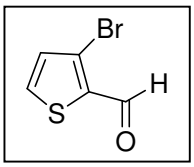



To a solution of methyl thiophene **153** (600 mg, 2.82 mmol) in $CCl_4$ (15 ml) was added NBS (503 mg, 2.82 mmol) and AIBN (20 mg, cat.). The reaction was heated at 80 °C for 3 h and then cooled and filtered to remove the succinimide. The crude organics concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 100:2.5–100:5) to afford thiophenemethyl bromide **154** as a yellow oil (384 mg, 53%).

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.43; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 2927, 1613, 1508; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.32 (1H, d, *J* 5.4, Het*H*), 6.95 (1H, d, *J* 5.4, Het*H*), 4.69 (2H, s, C*H*$_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 134.5 (C), 130.3 (CH), 126.6 (CH), 112.6 (C), 25.1 ($CH_3$).

$^1$H and $^{13}$C NMR spectroscopic data in good agreement with the literature.[104]

**3-Bromothiophene-2-carbaldehyde 156**[106]

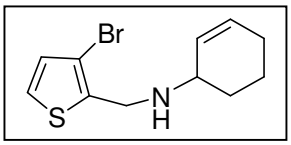



To a solution of diisopropylamine (7.03 ml, 50.0 mmol) in THF (80 ml) at 0 °C was added *n*BuLi (3.87 ml, 62.0 mmol, 1.6 M in hexanes) and the reaction stirred for 30 mins. 3-Bromothiophene (4.63 ml, 50.0 mmol) was added dropwise and the reaction was stirred for 30 mins. Freshly distilled DMF (3.87 ml, 50.0 mmol) was added dropwise and the reaction allowed to warm to r.t. and stirred for 2.5 h. The reaction was diluted with $Et_2O$ (80 ml) and the organics washed with $NH_4Cl$ (3 x 50 ml, sat. aq.), dried ($MgSO_4$), and concentrated under reduced pressure to afford aldehyde **156** as a yellow oil (8.85 g, 94%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.64; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1665 (C=O), 1498, 1416, 1213, 737; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 9.99 (1H, d, *J* 1.4, CO*H*), 7.75 (1H, dd, *J* 5.1, 1.4, Het*H*), 7.16 (1H, d, *J* 5.1, Het*H*); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 182.9 (C), 136.8 (C), 134.7 (CH), 131.9 (CH), 120.2 (C); ***m/z*** (FAB, THIOG) 283 (95), 281 (93), ([$^{81Br}$M+H]$^+$ 193, 96 %), ([$^{79Br}$M+H]$^+$ 191, 100), 177 (19), 175 (18), 109 (17); **HRMS** (FAB, THIOG) (Found: [$^{81Br}$M+H]$^+$, 192.9147. $C_5H_3N^{81}BrOS$ requires 192.9147). (Found: [$^{79Br}$M+H]$^+$ 190.9166. $C_5H_3N^{79}BrOS$ requires 190.9166).

$^1$H and $^{13}$C NMR spectroscopic data in good agreement with the literature.[106]

**(3-Bromo-thiophen-2-ylmethyl)-cyclohex-2-enyl-amine 155**

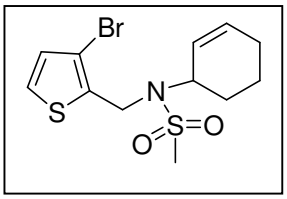



**Alkylation:** To a suspension of 3-aminocyclohexene hydrochloride[105] (53 mg, 0.39 mmol) in MeCN (5 ml) at 0 °C was added $^{i}Pr_2NEt$ (272 µl, 1.56 mmol), and the reaction was stirred for 5 mins. 3-Bromo-2-bromomethyl-thiophene **154** (100 mg, 0.39 mmol) was added and the reaction stirred for 16 h at r.t. The reaction was concentrated under reduced pressure and the residue taken up in $CH_2Cl_2$ (5 ml) and washed with NaCl (3 x 5 ml, sat. aq.). The organics were combined, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 10:1-5:1) to afford amine **155** as a brown oil (19 mg, 18%).

**Reductive amination:** To a suspension of 3-aminocyclohexene hydrochloride[105] (5.64 g, 31.7 mmol) in toluene (150 ml) was added $^{i}Pr_2NEt$ (6.90 ml, 26.5 mmol) and the reaction was stirred for 10 mins. Aldehyde **156** (5.00 g, 26.5 mmol) and molecular sieves (5.00 g) were added and the reaction was heated at reflux for 16 h. The reaction was concentrated under reduced pressure, and the crude imine was dissolved in methanol (150 ml), cooled to 0 °C and $Na(OAc)_3BH$ (33.6 g, 158.7 mmol) was added portionwise. The reaction was stirred at r.t. for 16 h then diluted with $CH_2Cl_2$ (150 ml) and washed with NaCl (3 x 50 ml, sat. aq.). The organics were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc:$NH_3$, 100:10:0.1) to afford amine **155** as a brown oil (1.18 g, 16%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.76; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3416 (NH), 1464, 1382, 1364; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.20 (1H, d, *J* 5.3, Het*H*), 6.93 (1H, d, *J* 5.2, Het*H*), 5.82-5.70 (2H, m, C*H*=C*H*), 4.02 (1H, d, *J* 15.1, $CH_XH_Y$Het), 3.96 (1H, d, *J* 15.1, $CH_XH_Y$Het), 3.24 (1H, br s, C*H*N), 2.13-1.84 (3H, m, $CH_2$+$CH_AH_B$), 1.82-1.72 (1H, m, $CH_AH_B$), 1.61-1.49 (2H, m, $CH_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 139.3 (C), 129.7 (CH), 129.5 (CH), 129.2 (CH), 124.2 (CH), 107.9 (C), 52.0 (CH), 44.6 ($CH_2$), 29.3 ($CH_2$), 25.2 ($CH_2$), 20.0 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 274 ([$^{81Br}$M+H]$^+$, 63 %), 272 ([$^{79Br}$M+H]$^+$, 69), 192 (78), 190 (46), 177 (80), 175 (78); **HRMS** (FAB, 3-NOBA) Found: [$^{81Br}$M+H]$^+$, 274.0086. $C_{11}H_{15}N^{81}BrS$ requires 274.0088.

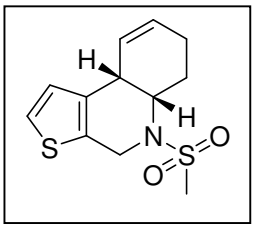
***N*-(3-Bromo-thiophen-2-ylmethyl)-*N*-cyclohex-2-enyl-methanesulfonamide 157**



General procedure **B** was followed using amine **155** (300 mg, 1.10 mmol), $CH_2Cl_2$ (10 ml), methanesulfonyl chloride (256 µl, 3.31 mmol) and $Et_3N$ (465 µl, 3.31 mmol). Flash chromatography (hexane:EtOAc, 10:1–3:1) afforded sulfonamide **157** as a yellow oil (262 mg, 68%).

**$R_f$** [hexane: EtOAc, 3:1] = 0.46; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1325, 1152, 745 **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.26 (1H, d, *J* 5.4, Het*H*), 6.88 (1H, d, *J* 5.4, Het*H*), 6.01-5.95 (1H, m, C*H*=CH), 5.54-5.49 (1H, m, CH=C*H*), 4.56 (1H, d, *J* 16.8, $CH_XH_Y$Het), 4.55-4.50 (1H, br s, C*H*N), 4.49 (1H, d, *J* 16.8, $CH_XH_Y$Het), 2.94 (3H, s, $CH_3$), 2.06-1.94 (3H, m, $CH_2$+$CH_AH_B$), 1.84-1.72 (1H, m, $CH_AH_B$), 1.62-1.59 (2H, m, $CH_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 137.8 (C), 133.6 (CH), 129.5 (CH), 126.8 (CH), 125.5 (CH), 108.8 (C), 55.6 (CH), 42.2($CH_2$), 40.3 ($CH_3$), 28.6 ($CH_2$), 24.3 ($CH_2$), 21.6 ($CH_2$); ***m/z*** (FAB, THIOG) 352([$^{81Br}$M+H]$^+$, 12 %), 350 ([$^{79Br}$M+H]$^+$, 15), 272 (25), 270 (37), 190 (34), 188 (56), 177 (73), 175 (74); **HRMS** (FAB, THIOG) Found: [$^{81Br}$M+H]$^+$, 351.9860. $C_{12}H_{17}N^{81}BrO_2S_2$ requires 351.9864. Found: [$^{79Br}$M+H]$^+$ 349.9848. $C_{12}H_{17}N^{79}BrO_2S_2$ requires 349.9884.

**(5a*SR*,9a*SR*)-5-Methanesulfonyl-3a,4,5,5a,6,7,9a,9b-octahydro-thieno[2,3-*c*]quinoline 158 ($\Delta^{1,2}$ isomer)**



**Cationic:** To a solution of cyclohexene **157** (50.0 mg, 0.14 mmol) in DMA (5 ml) was added $Pd(OAc)_2$ (1.6 mg, 7.0 µmol), $PCy_3$ (4.1 mg, 14.3 µmol) and $MeNCy_2$ (122 µl, 0.57 mmol) and the reaction was heated at 160 $^oC$ for 2 h. Flash chromatography (hexane:EtOAc, 10:1) afforded the quinoline as a colourless oil (23 mg, 60 %). $^1$H NMR of this oil showed it to be 77:16:7 mixture of double bond isomers (**158:159:160**). **Neutral:** General procedure **D** was followed using cyclohexene **157** (30 mg, 0.090 mmol), palladacycle **100** (4.0 mg, 4.3 µmol) and $MeNCy_2$ (73 µl, 0.34 mmol). Flash chromatography (hexane:EtOAc, 100:1-10:1) afforded the quinoline as a colourless oil (17 mg, 74 %). $^1$H NMR of this oil showed it to be 32:41:27 mixture of double bond isomers (**158:159:160**).

**$R_f$** [hexane:EtOAc, 3:1] = 0.41; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1447, 1325, 1151; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.21 (1H, d, *J* 5.1, Het*H*), 6.93 (1H, d, *J* 5.1, Het*H*), 6.05-6.01 (1H, m, C*H*=CH), 5.83-7.78 (1H, m, CH=C*H*), 4.82 (1H, dd, *J* 16.9, 0.9, C$H_X$$H_Y$Het), 4.42 (1H, dd, *J* 16.8, 1.8, CH$_X$$H_Y$Het), 4.36-4.32 (1H, m, C*H*N), 3.56 (1H, br s, NCHC*H*), 2.86 (3H, s, C$H_3$), 2.38-2.26 (1H, m, C$H_A$$H_B$), 2.22-2.10 (1H, m, CH$_A$$H_B$), 1.84-1.78 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 135.8 (C), 127.8 (CH), 126.4 (CH), 125.9 (CH), 123.9 (CH), 111.28 (C), 51.4 (CH), 40.4 ($CH_2$), 39.9 ($CH_3$), 35.8 (CH), 25.2 ($CH_2$), 23.2 ($CH_2$); ***m/z*** (FAB, THIOG) 270 ($[M+H]^+$, 50 %), 268 (73), 214 (32), 190 (69), 188 (72), 175 (32), 163 (33); **HRMS** (FAB, 3-NOBA) Found: $[M+H]^+$, 270.0628. $C_{12}H_{16}O_2NS_2$ requires 270.0623.

**Diagnostic $^1$H NMR data for 159 ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.22 (1H, d, *J* 5.2, Het*H*), 6.92 (1H, d, *J* 5.2, Het*H*), 5.65-5.61 (1H, m, C*H*=CH), 5.52-5.48 (1H, m, CH=C*H*), 4.83 (1H, d, *J* 16.3, C*H*xH$_Y$Het), 4.51 (1H, dd, *J* 16.3, 2.2, CH$_X$$H_Y$Het), 4.45-4.39 (1H, m, NC*H*), 3.29-3.25 (1H, m, NCHC*H*), 2.94 (3H, s, C$H_3$), 2.75-2.65 (2H, m, C$H_2$), 2.22-2.18 (2H, m, C$H_2$).

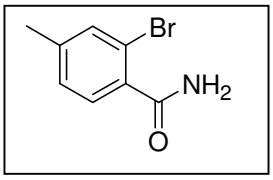
**Diagnostic $^1$H NMR data for 160 ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, $CDCl_3$) 5.87-5.80 (1H, m, C*H*=CH), 5.55-5.50 (1H, m, CH=C*H*), 4.86 (1H, br s, NC*H*), 4.73 (1H, d, *J* 16.6, C*H*xH$_Y$Het), 3.34 (1H, br s, NCHC*H*), 2.84 (3H, s, C$H_3$).

**General procedure F - Synthesis of aryl amide analogues**

A mixture of the appropriate benzoic acid (approx. 1.00 g) and thionyl chloride (15 ml) was refluxed at 60 $^{o}$C for 3 h. The thionyl chloride was removed under reduced pressure and the residue was dissolved in $NH_4OH$ (15 ml, conc.) and stirred for 16 h at r.t. The reaction was filtered and the precipitate dried on the high vacuum line for several hours to afford the desired amide.

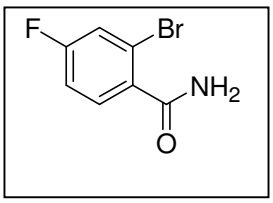
**2-Bromo-4-methylbenzamide 162a**[181]




General procedure **F** was followed using 2-bromo-4-methyl benzoic acid (800 mg, 3.70 mmol) and thionyl chloride (12 ml) to afford amide **162a** as a colourless solid (750 mg, 95%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.45; **MP** 171 $^{o}$C ($H_2O$), lit 175 $^{o}$C[181]; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3419 (NH), 1636 (C=O); **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.46 (1H, s, Ar*H*), 7.33 (1H, d, *J* 8.0, Ar*H*), 7.19 (1H, dd, *J* 7.5, 0.8, Ar*H*), 2.33 (3H, s, C*H*$_3$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 173.4 (C), 143.1 (C), 136.6 (C), 134.7 (CH), 129.7 (CH), 129.2 (CH), 120.0 (C), 20.9 ($CH_3$); ***m/z*** (FAB, 3-NOBA) 216 ([$^{81Br}$M+H]$^+$, 75 %), 214 ([$^{79Br}$M+H]$^+$, 77), 199 (10), 197 (10), 154 (100), 136 (100), 121 (27); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 214.9760. $C_8H_8ON^{81}Br$ requires 214.9763. Found: [$^{79Br}$M]$^+$, 212.9779. $C_8H_8ON^{79}Br$ requires 212.9784.

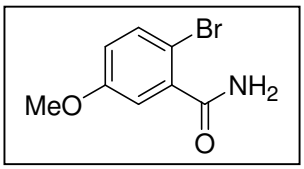
**2-Bromo-4-fluorobenzamide 162b**




General procedure **F** was followed using 2-bromo-4-fluoro benzoic acid (1.00 g, 4.57 mmol) and thionyl chloride (15 ml) to afford amide **162b** as a colourless solid (940 mg, 94%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.4; **MP** 155 $^{o}$C ($H_2O$); **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3400 (NH), 1639 (C=O); **$^1$H NMR** δ (360 MHz, $CD_3OD$) 7.50 (1H, dd, *J* 8.4, 5.8, Ar*H*), 7.46 (1H, dd, *J* 8.6, 2.6, Ar*H*), 7.22 (1H, td, *J* 8.4, 2.6, Ar*H*); **$^{13}$C NMR** δ (90.6 MHz, $CD_3OD$) 172.6 (C), 164.4 (1C, d, *J* 252.1, C), 136.5 (C), 131.7 (1C, d, *J* 9.0, CH), 121.7 (1C, d, *J* 25.1, CH), 121.2 (1C, d, *J* 9.9, C), 115.9 (1C, d, *J* 21.7, CH); ***m/z*** (FAB, 3-NOBA) 220 ([$^{81Br}$M+H]$^+$, 64 %), 218 ([$^{79Br}$M+H]$^+$, 66), 167 (12), 165 (11), 136 (100); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 218.9511. $C_7H_5ON^{81}BrF$ requires 218.9513. Found: [$^{79Br}$M]$^+$, 216.9528. $C_7H_5ON^{79}BrF$ requires 216.9533.

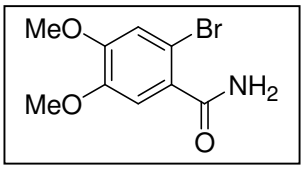
**2-Bromo-5-methoxybenzamide 162c**[182]




General procedure **F** was followed using 2-bromo-5-methoxy benzoic acid (1.00 g, 4.53 mmol) and thionyl chloride (15 ml) to afford amide **162c** as a colourless solid (650 mg, 65%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.45; **MP** 154 °C, lit 157 °C[182]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3415 (NH), 1635 (C=O); **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.53 (1H, d, *J* 8.8, Ar*H*), 7.04 (1H, d, *J* 3.3, Ar*H*), 6.95 (1H, dd, *J* 8.8, 3.3, Ar*H*), 3.84 (3H, s, C$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 160.1 (C), 150.8 (C), 134.7 (CH), 128.8 (C), 117.7 (CH), 115.0 (CH), 109.8 (C), 55.8 ($CH_3$); ***m/z*** (FAB, 3-NOBA) 232 ([$^{81Br}$M+H]$^+$, 65 %), 230 ([$^{79Br}$M+H]$^+$, 67), 154 (100), 136 (100), 121 (26), 109 (42); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 230.9715. $C_8H_8O_2N^{81}Br$ requires 230.9713. Found: [$^{79Br}$M]$^+$, 228.9733. $C_8H_8O_2N^{79}Br$ requires 228.9733.

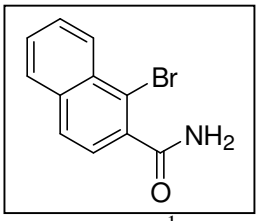
**2-Bromo-4,5-methoxybenzamide 162d**[183]




General procedure **F** was followed using 2-bromo-4,5-methoxy benzoic acid (2.00 g, 7.66 mmol) and thionyl chloride (30 ml) to afford amide **162d** as a colourless solid (1.45 g, 73%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.49; **MP** 178 °C, lit 178 °C[183]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3442 (NH), 1676 (C=O); **$^1$H NMR** δ (250 MHz, $(CD_3)_2SO$) 7.73 (1H, br s, N*H*), 7.48 (1H, br s, N*H*), 7.14 (1H, s, Ar*H*), 7.02 (1H, s, Ar*H*), 3.80 (3H, s, C$H_3$), 3.78 (3H, s, C$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $(CD_3)_2SO$) 167.9 (C), 149.1 (C), 147.0 (C), 129.9 (C), 115.1 (CH), 111.4 (CH), 108.6 (C), 55.3 ($CH_3$), 55.1 ($CH_3$); ***m/z*** (FAB, 3-NOBA) 262 ([$^{81Br}$M+H]$^+$, 100 %), 260 ([$^{79Br}$M+H]$^+$, 83), 245 (100), 243 (71), 204 (23), 202 (34), 200 (24), 181 (37), 180 (26), 167 (27), 166 (30); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 260.9825. $C_9H_{10}O_3N^{79}Br$ requires 260.9818. Found: [$^{79Br}$M]$^+$, 258.9838. $C_9H_{10}O_3N^{79}Br$ requires 258.9839.

**1-Bromo-naphthalene-2-carboxamide 162e**[184]

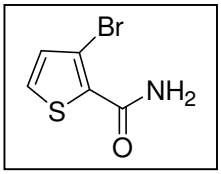



General procedure **F** was followed using 1-bromo-2-naphthoic acid (1.00 g, 3.98 mmol) and thionyl chloride (15 ml) to afford amide **162e** as a colourless solid (995 mg, 99%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.67; **MP** 202 $^oC$ ($H_2O$); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3440 (NH), 1678 (C=O); **$^1$H NMR** δ (250 MHz, $(CD_3)_2SO$) 8.20 (1H, d, *J* 7.5, Ar*H*), 8.17 (1H, br s, N*H*), 8.14 (2H, br s, 2xAr*H*), 7.88 (1H, br s, N*H*), *7*.84 (1H, td, *J* 6.8, 1.5, Ar*H*), 7.79 (1H, td, *J* 6.8, 1.5, Ar*H*), 7.62 (1H, d, *J* 6.8, Ar*H*); **$^{13}$C NMR** δ (62.9 MHz, $(CD_3)_2SO$) 169.4 (C), 137.7 (C), 133.4 (C), 130.8 (C), 128.1 (2xCH), 127.7 (CH), 127.0 (CH), 126.4 (CH), 124.6 (CH), 117.8 (C); ***m/z*** (FAB, 3-NOBA) 252 ([$^{81Br}$M+H]$^+$, 76 %), 250 ([$^{79Br}$M+H]$^+$, 90), 235 (12), 233 (13), 154 (100), 149 (26), 138 (41), 136 (97), 107 (46); **HRMS** (EI +ve) Found: [$^{81Br}$M]$^+$, 250.9765. $C_{11}H_8{}^{81}BrNO$ requires 250.9763. Found: [$^{79Br}$M]$^+$, 248.9782. $C_{11}H_8{}^{79}BrNO$ requires 248.9784.

$^1$H and $^{13}$C NMR data in good agreement with the literature.[184]

**3-Bromothiophene-2-carboxamide 162f**[185]

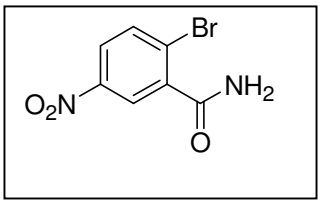



General procedure **F** was followed using 3-bromothiophene-2-carboxylic acid (1.00 g, 4.88 mmol) and thionyl chloride (15 ml) to afford amide **162f** as a beige solid (923 mg, 93%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.59; **MP** 102 $^oC$, lit 103 $^oC$[185]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3432 (NH), 1642 (C=O), 1429; **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.71 (1H, d, *J* 5.5, Het*H*), 7.16 (1H, d, *J* 5.5, Het*H*); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 167.0 (C), 143.0 (C), 134.1 (C), 132.7 (CH), 131.0 (CH); ***m/z*** (FAB, 3-NOBA) 208 ([$^{81Br}$M+H]$^+$, 66 %), 206 ([$^{79Br}$M+H]$^+$, 65), 154 (100), 138 (32), 137 (70), 136 (85); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 206.9169. $C_5H_4ON^{81}BrS$ requires 206.9171. Found: [$^{79Br}$M]$^+$, 204.9190. $C_5H_4ON^{79}BrS$ requires 204.9191.

$^1$H NMR data in good agreement with the literature.[185]

**2-Bromo-5-nitro-benzamide 162g**[186]

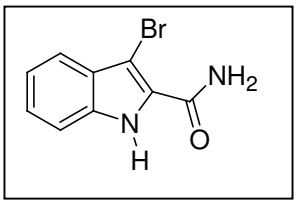



General procedure **F** was followed using 2-bromo-5-nitrobenzoic acid (2.00 g, 8.13 mmol) and thionyl chloride (30 ml) to afford amide **162g** as a colourless solid (1.99 g, 99%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.63; **MP** 168 °C, lit 197-198 °C (EtOH)[186]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3420 (NH), 1654 (C=O); **$^1$H NMR** δ (250 MHz, $(CD_3)_2SO$) 8.19 (1H, s, Ar*H*), 8.17 (1H, dd, *J* 8.7, 2.8, Ar*H*), 8.16 (1H, br s, NH), 7.98 (1H, td, *J* 8.8, 1.4, Ar*H*), 7.88 (1H, br s, N*H*); **$^{13}$C NMR** δ (62.9 MHz, $(CD_3)_2SO$) 167.5 (C), 146.8 (C), 140.6 (C), 134.9 (CH), 126.8 (C), 125.4 (CH), 123.4 (CH); ***m/z*** (FAB, 3-NOBA) 247 ([$^{81Br}$M+H]$^+$, 32 %), 245 ([$^{79Br}$M+H]$^+$, 33), 167 (22), 154 (100); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 245.9461. $C_7H_5{}^{81}BrN_2O_3$ requires 245.9458. Found: [$^{79Br}$M]$^+$, 243.9485. $C_7H_5{}^{79}BrN_2O_3$ requires 243.9478.

$^1$H and $^{13}$C spectroscopic data in agreement with literature.[186]

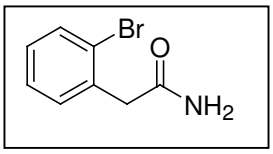
**3-Bromoindole-2-carboxylic acid amide 162h**




General procedure **F** was followed using 3-bromo-2-carboxylic acid (1.00 g, 4.17 mmol) and thionyl chloride (15 ml) to afford amide **162h** as a yellow solid (885 mg, 89%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.66; **MP** 173 °C; **$\upsilon_{max}$** ($(CH_3)_2SO$)/$cm^{-1}$ 3452 (NH), 1672 (C=O), 1619 (C=O); **$^1$H NMR** δ (250 MHz, $(CD_3)_2SO$) 12.0 (1H, br s, N*H*), 7.88 (1H, br s, N*H*), 7.46 (2H, t, *J* 7.8, 2xAr*H*), 7.31 (1H, br s, N*H*), 7.33-7.27 (1H, m, Ar*H*), 7.17 (1H, t, 8.1, Ar*H*); **$^{13}$C NMR** δ (62.9 MHz, $(CD_3)_2SO$) 161.2 (C), 134.9 (C), 128.3 (C), 126.6 (C), 124.8 (CH), 120.8 (CH), 119.5 (CH), 112.7 (CH), 90.7 (C); ***m/z*** (FAB, 3-NOBA) 241 ([$^{81Br}$M+H]$^+$, 61 %), 239 ([$^{79Br}$M+H]$^+$, 61), 223 (46), 221 (44), 165 (37), 152 (55), 138 (64), 125 (43), 109 (73); **HRMS** (ES, 3-NOBA) Found: [$^{79Br}$M]$^+$, 238.9814. $C_9H_8{}^{79}BrN_2O$ requires 238.9815.

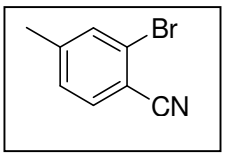
**2-(2'-bromophenyl)acetamide 162j**[187]




General procedure **F** was followed using 2-bromophenethyl carboxylic acid (3.00 g, 14.0 mmol) and thionyl chloride (30 ml) to afford amide **162j** as a colourless solid (2.20 g, 74%).

**$R_f$** [$CH_2Cl_2$: MeOH, 95:5] = 0.65; **MP** 184 °C (lit 184-186 °C)[187]; **$\upsilon_{max}$** ($(CH_3)_2SO$)/$cm^{-1}$ 3452 (NH), 1683 (C=O), 1635 (C=O); **$^1$H NMR** δ (250 MHz, $(CD_3)_2SO$) 7.58 (1H, d, *J* 7.5, Ar*H*), 7.47 (1H, br s, N*H*), 7.38-7.29 (2H, m, 2xAr*H*), 7.19 (1H, dd, *J* 8.0, 2.8, Ar*H*), 7.17 (1H, dd, *J* 7.8, 2.5, Ar*H*), 7.00 (1H, br s, N*H*); **$^{13}$C NMR** δ (62.9 MHz, $(CD_3)_2SO$) 170.2 (C), 135.4 (C), 131.5 (CH), 131.3 (CH), 127.8 (CH), 126.8 (CH), 123.8 (C), 41.4 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 216 ([$^{81Br}$M+H]$^+$, 72 %), 214 ([$^{79Br}$M+H]$^+$, 72 ), 180 (21), 171 (52), 169 (61), 154 (77), 150 (41), 136 (79); **HRMS** (ESI+) Found: [$^{79Br}$M+$NH_4$]$^+$, 231.0128. $C_8H_{12}{}^{79}BrN_2O$ requires 231.0128.

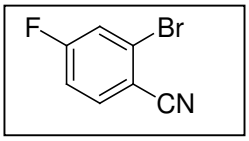
**2-Bromo-4-methyl benzonitrile 163a**[188]




A mixture of amide **162a** (750 mg, 3.50 mmol) and thionyl chloride (5 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile **163a** as a colourless solid (500 mg, 73%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.75; **MP** 55 °C, lit 56 °C[188]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3408, 2230 (CN); **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.38-7.37 (2H, m, 2xAr*H*), 7.34 (1H, dq, *J* 8.0, 1.5, Ar*H*), 2.43 (3H, s, C$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 146.8 (C), 134.6 (CH), 134.2 (CH), 129.3 (CH), 124.9 (C), 117.5 (C), 112.9 (C), 20.8 ($CH_3$); ***m/z*** (FAB, 3-NOBA) 198 ([$^{81Br}$M+H]$^+$, 47 %), 196 ([$^{79Br}$M+H]$^+$, 48), 167 (13), 165 (12), 154 (100); **HRMS** (ES, 3-NOBA) Found: [$^{81Br}$M]$^+$, 196.9656. $C_8H_6{}^{81}BrN$ requires 196.9658. Found: [$^{79Br}$M]$^+$, 194.9678. $C_8H_6{}^{79}BrN$ requires 194.9678.

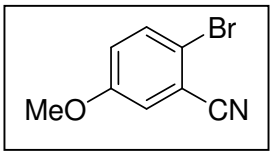
**2-Bromo-4-fluorobenzonitrile 163b**




A mixture of amide **162b** (940 mg, 4.30 mmol) and thionyl chloride (6 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile **163b** as a colourless solid (840 mg, 97%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.78; **MP** 76 °C (EtOH); **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2228 (CN); **$^1$H NMR** δ (360 MHz, $CD_3OD$) 7.88 (1H, dd, *J* 8.6, 5.4, Ar*H*), 7.69 (1H, dd, *J* 8.3, 2.5, Ar*H*), 7.35 (1H, td, *J* 8.6, 2.5, Ar*H*); **$^{13}$C NMR** δ (90.6 MHz, $CD_3OD$) 166.4 (1C, d, *J* 259.3, C), 138.0 (1C, d, *J* 10.1, CH), 127.6 (1C, d, *J* 10.3, C), 122.5 (1C, d, *J* 26.1, CH), 117.6 (C), 117.3 (1C, d, *J* 22.9, CH), 113.5 (C); ***m/z*** (FAB, 3-NOBA) 202 ([$^{81Br}$M+H]$^+$, 3 %), 200 ([$^{79Br}$M+H]$^+$, 2), 154 (64), 121 (11); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 200.9407. $C_7H_3{}^{81}BrFN$ requires 200.9407. Found: [$^{79Br}$M]$^+$, 198.9422. $C_7H_3{}^{79}BrFN$ requires 198.9427.

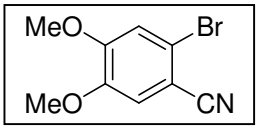
**2-Bromo-5-methoxybenzonitrile 163c**[189]




A mixture of amide **162c** (630 mg, 2.74 mmol) and thionyl chloride (3 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile **163c** as a colourless solid (510 mg, 88%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.74; **MP** 95 °C, lit 98.5-99.5 °C[189]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3420, 2229 (CN); **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.67 (1H, d, *J* 9.0, Ar*H*), 7.38 (1H, d, *J* 3.1, Ar*H*), 7.18 (1H, dd, *J* 9.0, 3.1, Ar*H*), 3.89 (3H, s, $CH_3$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 161.3 (C), 134.9 (CH), 121.9 (CH), 120.0 (CH), 117.6 (C), 116.7 (C), 115.7 (C), 56.2 ($CH_3$); ***m/z*** (FAB, 3-NOBA) 214 ([$^{81Br}$M+H]$^+$, 8 %), 212 ([$^{79Br}$M+H]$^+$, 8), 167 (20), 165 (26), 154 (100); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 212.9604. $C_8H_6{}^{81}BrNO$ requires 212.9607. Found: [$^{79Br}$M]$^+$, 210.9622. $C_8H_6{}^{79}BrNO$ requires 210.9627.

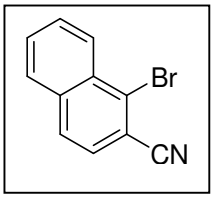
**2-Bromo-4,5-methoxybenzonitrile 163d**[190]




A mixture of amide **162d** (1.25 g, 4.81 mmol) and thionyl chloride (30 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile **163d** as a colourless solid (1.15 g, 99%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.5; **MP** 113 °C (EtOH), lit 117 °C[**190**]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2229 (CN); **$^1$H NMR** δ (250 MHz, $(CD_3)_2SO$) 7.49 (1H, s, Ar*H*), 7.39 (1H, s, Ar*H*), 3.87 (3H, s, C$H_3$), 3.81 (3H, s, C$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $(CD_3)_2SO$) 153.4 (C), 148.5 (C), 117.9 (C), 116.9 (C), 116.2 (CH), 115.9 (CH), 105.4 (C), 56.8 ($CH_3$), 56.3 ($CH_3$); ***m/z*** (FAB, 3-NOBA) 244 ([$^{81Br}$M+H]$^+$, 27 %), 242 ([$^{79Br}$M+H]$^+$, 42), 167 (16), 154 (98), 152 (17), 150 (15), 149 (49), 137 (82), 136 (74); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 242.9708. $C_9H_8{}^{81}BrNO_2$ requires 242.9713. Found: [$^{79Br}$M]$^+$, 240.9726. $C_9H_8{}^{79}BrNO_2$ requires 240.9733.

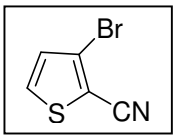
**1-Bromo-2-naphthalene-2-carbonitrile 163e**[191]




A mixture of amide **162e** (950 mg, 3.80 mmol) and thionyl chloride (6 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile **163e** as a colourless solid (839 mg, 95%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.83; **MP** 91 °C (EtOH), lit 93 °C[**191**]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2226 (CN), 1580 (C=C), 1560 (C=C); **$^1$H NMR** δ (250 MHz, $CD_3OD$) 8.33-8.29 (1H, m, Ar*H*), 8.04-7.98 (2H, m, 2xAr*H*), 7.80-7.72 (2H, m, 2xAr*H*), 7.66 (1H, d, *J* 8.5, Ar*H*); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 136.3 (C), 132.1 (C), 130.2 (CH), 129.6 (CH), 129.5 (CH), 129.2 (CH), 128.3 (CH), 128.2 (C), 127.9 (CH), 118.2 (C), 113.9 (C); ***m/z*** (FAB, 3-NOBA) 234 ([$^{81Br}$M+H]$^+$, 27 %), 232 ([$^{79Br}$M+H]$^+$, 27), 154 (99), 138 (48), 136 (100); **HRMS** (EI +ve) Found: [$^{81Br}$M]$^+$, 232.9656. $C_{11}H_6N^{81}Br$ requires 232.9658. Found: [$^{79Br}$M]$^+$, 230.9680. $C_{11}H_6N^{79}Br$ requires 230.9678.

**3-Bromothiophene-2-carbonitrile 163f**[192]

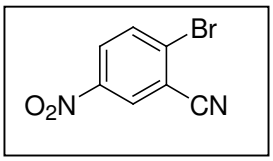



A mixture of amide **162f** (920 mg, 4.48 mmol) and thionyl chloride (3 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile **163f** as a brown oil (840 mg, 99%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.52; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3109, 2221 (CN), 1407; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.53 (1H, d, *J* 5.3, Het*H*), 7.07 (1H, d, *J* 5.3, Het*H*); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 132.7 (CH), 130.7 (CH), 121.7 (C), 112.6 (C), 108.5 (C); ***m/z*** (FAB, 3-NOBA) 189 ([$^{81Br}$M+H]$^+$, 3 %), 187 ([$^{79Br}$M+H]$^+$, 1), 165 (12), 154 (100), 149 (30), 138 (80), 137 (98), 136 (100), 125 (29); **HRMS** (FAB, 3-NOBA) Found: [$^{81Br}$M+H]$^+$, 188.9066. $C_5H_2{}^{81}BrNS$ requires 188.9065. Found: [$^{79Br}$M+H]$^+$, 186.9086. $C_5H_2{}^{79}BrNS$ requires 186.9086.

$^1$H NMR data in good agreement with the literature.[192]

**2-Bromo-5-nitro-benzonitrile 163g**[193]



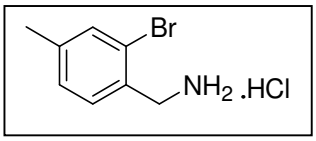

A mixture of amide **162g** (1.30 g, 5.29 mmol) and thionyl chloride (30 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile **163g** as a colourless solid (1.20 g, 99%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.91; **MP** 108 °C, lit 117 °C ($H_2O$)[193]; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2253 (CN); **$^1$H NMR** δ (250 MHz, $(CD_3)_2SO$) 8.85 (1H, d, *J* 2.7, Ar*H*), 8.42 (1H, dd, *J* 8.9, 2.7, Ar*H*), 8.20 (1H, d, *J* 8.9, Ar*H*); **$^{13}$C NMR** δ (90.6 MHz, $(CD_3)_2SO$) 147.8 (C), 135.6 (CH), 133.1 (C), 130.8 (CH), 130.1 (CH), 116.9 (C), 116.7 (C).

**General procedure G - Reduction of aryl nitrile analogues**

To a suspension of $LiAlH_4$ (2 eq) in $Et_2O$ (10 ml) was added $AlCl_3$ (2 eq) and the reaction stirred for 10 mins at r.t. The mixture was cooled to 0 $^oC$ and the appropriate nitrile (1 eq) was added portionwise. The reaction was stirred at r.t for 30 mins then heated at 40 $^oC$ for 18 h. The reaction was quenched by the addition of $Na_2SO_4.5H_2O$ portionwise, then it was filtered and the filtrate stirred vigorously with potassium sodium tartrate (100 ml, sat. aq.) for 1 h. The $Et_2O$ layer was separated and the aqueous phase extracted with $Et_2O$ (3 x 60 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2$ (1 ml), and HCl in $Et_2O$ (20.0 ml, 1 M in $Et_2O$) added. The precipitate was removed by filtration and dried to afford the desired amine hydrochloride.

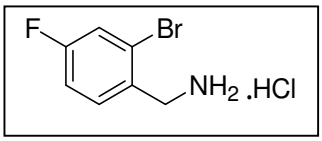
**2-Bromo-4-methylbenzylamine hydrochloride 164a**




General procedure **G** was followed using $LiAlH_4$ (186 mg, 4.90 mmol), $Et_2O$ (5 ml), $AlCl_3$ (654 mg, 4.90 mmol) and nitrile **163a** (480 mg, 2.45 mmol), to afford amine hydrochloride **164a** as a colourless solid (465 mg, 80%).

**MP** 249 $^oC$ ($Et_2O$); **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.53 (1H, s, Ar*H*), 7.43 (1H, d, *J* 8.0, Ar*H*), 7.27 (1H, d, *J* 8.0, Ar*H*), 4.23 (2H, s, C$H_2$), 2.35 (3H, s, C$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 142.8 (C), 134.4 (CH), 131.5 (CH), 130.5 (C), 129.9 (CH), 124.7 (C), 43.6 ($CH_2$), 20.5 ($CH_3$); ***m/z*** (FAB, 3-NOBA) 202 ([$^{81Br}$M+H]$^+$, 91 %), 200 ([$^{79Br}$M+H]+, 93), 185 (95), 183 (95),154 (51); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 200.9969. $C_8H_{10}{}^{81}BrN$ requires 200.9971. Found: [$^{79Br}$M]$^+$, 198.9985 $C_8H_{10}{}^{79}BrN$ requires 198.9991. **Free Amine: $R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.46; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3371 (NH), 3304 (NH), 2922, 1605, 1488; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.33 (1H, s, Ar*H*), 7.19 (1H, d, *J* 7.7, Ar*H*), 7.05 (1H, d, *J* 7.7, Ar*H*), 3.81 (2H, s, C$H_2$), 2.27 (3H, s, C$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 138.4 (C), 137.6 (C), 132.4 (CH), 128.0 (CH), 127.6 (CH), 122.4 (C), 45.8 ($CH_3$), 19.8 ($CH_2$).

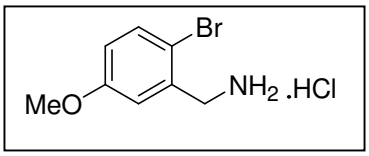
**2-Bromo-4-fluorobenzylamine hydrochloride 164b**




General procedure **G** was followed using $LiAlH_4$ (95 mg, 2.50 mmol), $Et_2O$ (5 ml), $AlCl_3$ (334 mg, 2.50 mmol) and nitrile **163b** (249 mg, 1.25 mmol) to afford amine hydrochloride **164b** as a colourless solid (210 mg, 70%).

**MP** 251 $^oC$ ($Et_2O$); **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.63 (1H, dd, *J* 8.8, 6.0, Ar*H*), 7.58 (1H, dd, *J* 8.3, 2.8, Ar*H*), 7.28 (1H, td, *J* 8.5, 2.8, Ar*H*), 4.29 (2H, s, C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 163.5 (1C, d, *J* 252.4, C), 133.1 (1C, d, *J* 9.0, CH), 129.6 (C), 125.3 (1C, d, *J* 10.3, C), 120.9 (1C, d, *J* 25.1, CH), 115.9 (1C, d, 21.6, CH), 42.8 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 206 ([$^{81Br}$M+H]$^+$, 14 %), 204 ([$^{79Br}$M+H]$^+$, 17), 189 (37), 187 (40), 149 (47); **HRMS** (ESI, +, $CH_2Cl_2$/MeOH/$NH_4OAc$) Found: [M+H]$^+$, 203.9820. $C_7H_8NF^{79}Br$ requires 203.9819. **Free Amine: $R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.46; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3285 (NH), 2926, 1597, 1484; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.33 (1H, dd, *J* 8.5, 6.0, Ar*H*), 7.26 (1H, dd, *J* 8.3, 2.5, Ar*H*), 6.98 (1H, td, *J* 8.3, 2.5, Ar*H*), 3.85 (2H, s, C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 160.6 (1C, d, *J* 249.3, C), 137.4 (C), 129.1 (1C, d, *J* 7.9, CH), 122.6 (1C, d, *J* 9.6, C), 119.1 (1C, d, *J* 24.8, CH), 113.9 (1C, d, *J* 20.8, CH), 45.4 ($CH_2$).

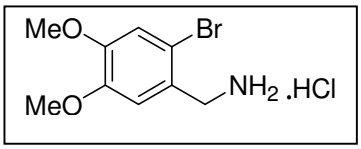
**2-Bromo-5-methoxybenzylamine hydrochloride 164c**




General procedure **G** was followed using $LiAlH_4$ (36.0 mg, 0.94 mmol), $Et_2O$ (1.00 ml), $AlCl_3$ (432 mg, 0.94 mmol) and nitrile **163c** (100 mg, 0.47 mmol), to afford amine hydrochloride **164c** as a colourless solid (301 mg, 74%).

**MP** 201 °C; **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.62 (1H, d, *J* 8.9, Ar*H*), 7.19 (1H, d, *J* 3.0, Ar*H*), 6.99 (1H, dd, *J* 8.9, 3.0, Ar*H*), 4.27 (2H, s, C$H_2$), 3.87 (3H, s, C$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 160.6 (C), 146.3 (C), 134.7 (CH), 117.2 (CH), 117.1 (CH), 114.5 (C), 55.7 ($CH_3$), 43.7 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 218 ([$^{81Br}$M+H]$^+$, 51 %), 216 ([$^{79Br}$M+H]$^+$, 62), 201 (39), 199 (40), 154 (100), 149 (43), 137 (59); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 216.9915. $C_8H_{10}ON^{81}Br$ requires 216.9920. Found: [$^{79Br}$M]$^+$, 214.9935. $C_8H_{10}ON^{79}Br$ requires 214.9940. **Free Amine: $R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.36; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3370 (NH), 1593, 1573, 1470, 1242; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.40 (1H, d, *J* 8.7, Ar*H*), 6.93 (1H, d, *J* 3.0, Ar*H*), 6.66 (1H, dd, *J* 8.7, 3.0, Ar*H*), 3.84 (2H, s, C$H_2$), 3.78 (3H, s, C$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 158.8 (C), 142.7 (C), 132.9 (CH), 114.3 (CH), 113.4 (CH), 113.2 (C), 55.0 ($CH_3$), 46.6 ($CH_2$).

**2-Bromo-4,5-methoxybenzylamine hydrochloride 164d**[194]

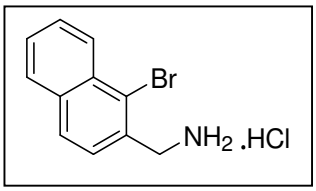



General procedure **G** was followed using $LiAlH_4$ (345 mg, 4.50 mmol), $Et_2O$ (20 ml), $AlCl_3$ (1.21 g, 9.00 mmol) and nitrile **163d** (1.10 g, 4.50 mmol), to afford amine hydrochloride **164d** as a colourless solid (829 mg, 65%).

**MP** 194 $^oC$; **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.25 (1H, s, Ar*H*), 7.21 (1H, s, Ar*H*), 4.25 (2H, s, C$H_2$), 3.90 (3H, s, C$H_3$), 3.88 (3H, s, C$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 151.8 (C), 150.2 (C), 125.2 (C), 116.8 (CH), 115.4 (C), 114.9 (CH), 56.5 (2x$CH_3$), 43.7 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 248 ($[^{81Br}M+H]^+$, 11 %), 246 ($[^{79Br}M+H]^+$, 20), 231 (37), 229 (37), 154 (82), 149 (64), 136 (100); **HRMS** (EI) Found: $[^{81Br}M]^+$, 247.0016. $C_9H_{12}O_2N^{81}Br$ requires 247.0026. Found: $[^{79Br}M]^+$, 245.0034. $C_9H_{12}O_2N^{79}Br$ requires 245.0046. **Free Amine: $R_f$** [$CH_2Cl_2$:MeOH, 95: 5] = 0.54; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3368 (NH), 2935, 2841, 1602, 1505; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.20 (1H, s, Ar*H*), 7.11 (1H, s, Ar*H*), 4.08 (3H, s, C$H_3$), 4.05 (3H, s, C$H_3$), 4.03 (2H, s, C$H_2$), 1.75 (2H, br s, N$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 148.2 (C), 148.0 (C), 133.9 (C), 115.3 (CH), 112.8 (C), 111.7 (CH), 55.8 ($CH_3$), 55.7 ($CH_3$), 46.2 ($CH_2$).

$^1$H and $^{13}$C NMR data in good agreement with the literature.[194]

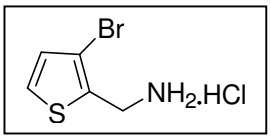
**(1-Bromo-2-naphthalen-2-yl) methyl amine hydrochloride 164e**




General procedure **G** was followed using $LiAlH_4$ (261 mg, 6.89 mmol), $Et_2O$ (10 ml), $AlCl_3$ (920 mg, 6.89 mmol) and nitrile **163e** (800 mg, 3.45 mmol), to afford amine hydrochloride **164e** as a colourless solid (504 mg, 55%).

**MP** 270 $^oC$ ($Et_2O$); **$^1$H NMR** δ (250 MHz, $CD_3OD$) 8.37 (1H, d, *J* 9.3, Ar*H*), 8.01 (1H, t, *J* 8.5, Ar*H*), 7.98 (1H, d, *J* 9.5, Ar*H*), 7.75-7.63 (3H, m, 3xAr*H*), 4.54 (2H, s, C*H*$_2$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 136.5 (C), 133.9 (C), 132.3 (C), 130.4 (CH), 130.0 (CH), 129.9 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 126.4 (C) 45.7 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 238 ([$^{81Br}$M+H]$^+$, 77 %), 236 ([$^{79Br}$M+H]$^+$, 43), 221 (97), 219 (97)167 (37), 165 (28), 154 (100); **HRMS** (EI +ve) Found: [$^{81Br}$M]$^+$, 236.9974. $C_{11}H_{10}N^{81}Br$ requires 236.9971. Found: [$^{79Br}$M]$^+$, 235.0001. $C_{11}H_{10}N^{79}Br$ requires 234.9991. **Free Amine: $R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.94; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3364 (NH), 1596 ($NH_2$); **$^1$H NMR** δ (250 MHz, $CDCl_3$) 8.15 (1H, d, *J* 8.5, Ar*H*), 7.62 (2H, t, *J* 7.5, 2xAr*H*), 7.42-7.29 (3H, m, 3xAr*H*), 3.96 (2H, s, C*H*$_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 140.0 (C), 133.5 (C), 132.2 (C), 127.9 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 126.0 (CH), 122.9 (C), 47.7 ($CH_2$).

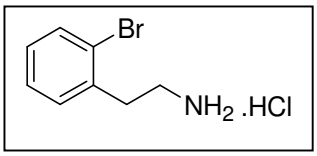
**(3-Bromo-2-thiophen-2-yl) methylamine hydrochloride 164f**




General procedure **G** was followed using $LiAlH_4$ (263 mg, 6.92 mmol), $Et_2O$ (7 ml), $AlCl_3$ (924 mg, 6.92 mmol) and nitrile **163f** (651 mg, 3.46 mmol) to afford amine hydrochloride **164f** as a beige solid (700 mg, 89%).

**MP** 187 °C; **$^1$H NMR** δ (250 MHz, $CD_3OD$) 7.68 (1H, d, *J* 5.3, Het*H*), 7.14 (1H, d, *J* 5.3, Ar*H*), 4.36 (2H, s, C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CD_3OD$) 130.9 (CH), 130.4 (C), 128.8 (CH), 113.7 (C), 37.2 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 194 ([$^{81Br}$M+H]$^+$, 20 %), 192 ([$^{79Br}$M+H]$^+$, 28), 177 (33), 175 (32), 154 (96), 138 (34), 137 (59), 136 (81); **HRMS** (EI) Found: [$^{81Br}$M]$^+$, 192.9376. $C_5H_6{}^{81}BrNS$ requires 192.9378. Found: [$^{79Br}$M]$^+$, 190.9393. $C_5H_6{}^{79}BrNS$ requires 190.9399. **Free Amine: $R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.80; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3370 (NH), 1594, 1344; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.30 (1H, d, *J* 5.3, Het*H*), 7.06 (1H, d, *J* 5.3, Het*H*), 4.09 (2H, s, C$H_2$), 1.86 (2H, br s, N$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 140.7 (C), 129.5 (CH), 123.3 (CH), 106.9 (C), 39.9 ($CH_2$).

**2-(2'-Bromophenyl) ethylamine hydrochloride 164j**[195]



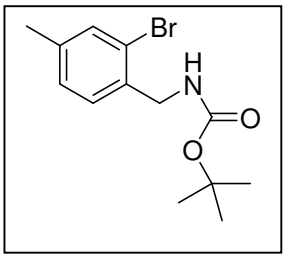

To a suspension of $LiAlH_4$ (709 mg, 18.7 mmol) in THF (15 ml) at 0 °C was added a solution of amide **162j** in THF (2 ml) dropwise. The reaction was stirred at r.t. for 30 mins then heated at 70 °C for 18 h. The reaction was quenched by the addition of $Na_2SO_4.5H_2O$ portionwise, then it was filtered and the filtrate stirred vigorously with potassium sodium tartrate (50 ml, sat. aq.) for 1 h. The $Et_2O$ layer was separated and the aqueous phase extracted with $Et_2O$ (3 x 20 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2$ (1 ml), and HCl in $Et_2O$ (10.0 ml, 1 M in $Et_2O$) added. The precipitate was filtered and dried to afford amine hydrochloride **164j** as a colourless solid (698 mg, 75%).

**MP** 203 °C; **$^1$H NMR** δ (360 MHz, $CD_3OD$) 7.66 (1H, dd, *J* 7.8, 0.6, Ar*H*), 7.44-7.38 (2H, m, 2xAr*H*), 7.24-7.23 (1H, m, Ar*H*), 3.22-3.16 (4H, m, 2x$CH_2$); **$^{13}$C NMR** δ (90.6 MHz, $CD_3OD$) 135.4 (C), 132.4 (CH), 130.3 (CH), 128.5 (CH), 127.5 (CH), 123.3 (C) 38.4 ($CH_2$), 33.0 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 202 ([$^{81Br}$M+H]$^+$, 85 %), 200 ([$^{79Br}$M+H]$^+$, 91), 185 (33), 183 (34), 165 (47), 154 (100), 137 (100); **HRMS** (ESI+) Found: [$^{79Br}$M]$^+$, 200.0070. $C_8H_{11}N^{79}Br$ requires 200.0070.

**General procedure H - Boc protection of aryl analogues**

To a suspension of the appropriate amine hydrochloride (1 eq) in $CH_2Cl_2$ (10 ml) was added $Et_3N$ (1.5 eq) and the reaction stirred for 10 mins. The reaction was cooled to 0 $^oC$, $Boc_2O$ (1.1 eq) added and the reaction allowed to warm to r.t. and stirred for 4 h. The reaction was diluted with $CH_2Cl_2$ (15 ml) and washed with NaCl (3 x 15 ml, sat. aq.). The organics were combined, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography to afford the desired carbamate.

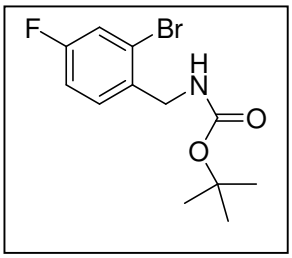
**2-Bromo-4-methylbenzyl-*tert*-butylcarboxamide 168a**




General procedure **H** was followed using amine hydrochloride **164a** (170 mg, 0.72 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (222 µl, 1.58 mmol) and $Boc_2O$ (173 mg, 0.79 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate **168a** as a colourless oil (217 mg, 100%).

**$R_f$** [3: 1 hexane: EtOAc] = 0.78; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3346 (NH), 2978, 2928, 1700 (C=O), 1506, 1365, 1250, 1172; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.36 (1H, s, Ar*H*), 7.25 (1H, d, *J* 7.8, Ar*H*), 7.07 (1H, dd, *J* 7.8, 0.9, Ar*H*), 4.98 (1H, br s, C*H*N), 4.34 (2H, d, *J* 6.2, C$H_2$Ar), 2.30 (3H, s, C$H_3$), 1.43 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.6 (C), 138.9 (C), 135.0 (C), 133.0 (CH), 129.4 (CH), 128.2 (CH), 123.2 (C), 79.3 (C), 44.6 ($CH_2$), 28.3 (3x$CH_3$), 20.4 ($CH_3$); ***m/z*** (EI) 302 ([$^{81Br}$M+H]$^+$, 2 %), 300 ([$^{79Br}$M+H]$^+$, 2), 244 (7), 242 (7); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 299.0516. $C_{13}H_{18}$ $^{79}$$BrNO_2$ requires 299.0515.

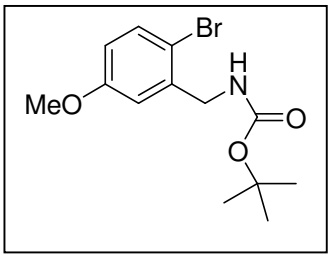
**2-Bromo-4-fluorobenzyl *tert*butylcarboxamide 168b**



General procedure **H** was followed using amine hydrochloride **164b** (167 mg, 0.69 mmol), $CH_2Cl_2$ (8 ml), $Et_3N$ (195 µl, 1.39 mmol) and $Boc_2O$ (167 mg, 0.76 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate **168b** as a colourless oil (184 mg, 88%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.85; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3343 (NH), 1696 (C=O); **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.35 (1H, dd, *J* 8.3, 6.0, Ar*H*), 7.27 (1H, dd, *J* 8.3, 2.5, Ar*H*), 6.99 (1H, dt, *J* 8.3, 2.5, Ar*H*), 5.11 (1H, br s, *CH*N), 4.33 (2H, d, *J* 6.3, C$H_2$Ar), 1.44 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 163.4 (C), 157.5 (1C, d, *J* 245.8, C), 133.8 (C), 130.5 (1C, d, *J* 7.8, CH), 123.2 (1C, d, *J* 9.6, C), 119.8 (1C, d, *J* 24.5, CH), 114.4 (1C, d, *J* 20.9, C), 79.6 (C), 44.0 ($CH_2$), 28.2 (3x$CH_3$); ***m/z*** (EI) 306 ([$^{81Br}$M+H]$^+$, 1 %), 304 ([$^{79Br}$M+H]$^+$, 1), 248 (14), 246 (13), 189 (17), 187 (18) 168 (100); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 303.0279. $C_{12}H_{15}{}^{79}BrFNO_2$ requires 303.0265.

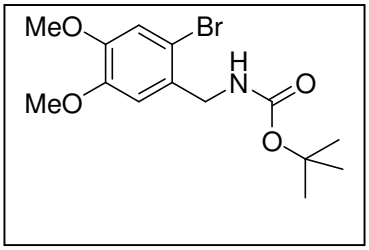
**2-Bromo-5-methoxybenzyl-*tert*butylcarboxamide 168c**



General procedure **H** was followed using amine hydrochloride **164c** (218 mg, 0.86 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (182 µl, 1.30 mmol) and $Boc_2O$ (207 mg, 0.95 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate **168c** as a colourless oil (230 mg, 85%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.77; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3350 (NH), 2977, 1698 (C=O), 1506, 1471; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.40 (1H, d, *J* 8.7, Ar*H*), 6.93 (1H, d, *J* 3.1, Ar*H*), 6.68 (1H, dd, *J* 8.7, 3.1, Ar*H*), 5.00 (1H, br s, N*H*), 4.33 (2H, d, *J* 6.3, C$H_2$Ar), 3.77 (3H, s, C$H_3$),1.46 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 159.2 (C), 155.6 (C), 139.0 (C), 133.1 (CH), 115.2 (CH), 114.6 (CH), 113.6 (C), 79.5 (C), 55.4 ($CH_3$), 45.0 ($CH_2$), 28.3 (3x$CH_3$); ***m/z*** (EI) 317 ([$^{81Br}$M]$^+$, 1 %), 315 ([$^{79Br}$M]$^+$, 1), 261 (3), 259 (3), 201 (9), 199 (10), 180 (100); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 315.0461. $C_{13}H_{18}{}^{79}BrNO_3$ requires 315.0465.

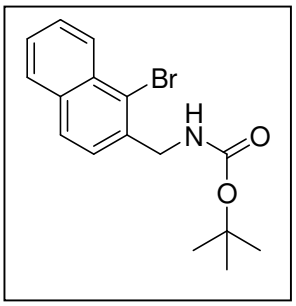
**(2-Bromo-4,5-dimethoxy-benzyl)-carbamic acid *tert*-butyl ester 168d**




General procedure **H** was followed using amine hydrochloride **164d** (200 mg, 0.710 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (219 µl, 1.56 mmol) and $Boc_2O$ (155 mg, 0.710 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate **168d** as a colourless oil (267 mg, 100%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.63; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3377 (NH), 1701 (C=O); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 6.93 (1H, s, Ar*H*), 6.85 (1H, s, Ar*H*), 5.07 (1H, br s, C*H*N), 4.24 (2H, d, *J* 6.0, C$H_2$Ar), 3.79 (6H, s, 2xC$H_3$), 1.39 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 155.7 (C), 149.1 (C), 148.7 (C), 130.4 (CH), 115.9 (CH), 113.4 (C), 113.2 (C), 79.5 (C), 56.2 ($CH_3$), 56.1 ($CH_3$), 44.7 ($CH_2$), 28.3 (3x$CH_3$); ***m/z*** (EI) 347 ([$^{81Br}$M]$^+$, 4 %), 345 ([$^{79Br}$M]$^+$, 4), 290 (27), 288 (27), 242 (13), 210 (100); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 345.0570. $C_{14}H_{20}{}^{79}BrNO_4$ requires 345.0570.

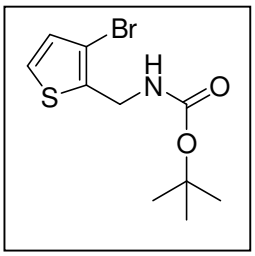
**(1-Bromo-naphthalen-2-ylmethyl) carbamic acid *tert*-butyl ester 168e**




General procedure **H** was followed using amine hydrochloride **164e** (200 mg, 0.73 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (155 µl, 1.10 mmol) and $Boc_2O$ (176 mg, 0.81 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate **168e** as a colourless solid (222 mg, 90%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.64; **MP** 96 $^oC$; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3346 (NH), 1699 (C=O), 1503, 1172; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 8.21 (1H, d, *J* 8.5, Ar*H*), 7.72 (1H, d, *J* 7.3, Ar*H*), 7.69 (1H, d, *J* 8.3, Ar*H*), 7.53-7.39 (3H, m, 3xAr*H*), 5.09 (1H, br s, N*H*), 4.54 (2H, d, *J* 6.3, C$H_2$), 1.37 (9H, s, 3xC$H_3$);**$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 155.7 (C), 136.0 (C), 133.7 (C), 132.2 (C), 128.0 (CH), 127.8 (CH), 127.4 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 123.4 (C), 79.6 (C), 45.7 ($CH_2$), 28.3 (3x$CH_3$); ***m/z*** (EI) 337 ([$^{81Br}$M+H]$^+$, 1 %), 335 ([$^{79Br}$M+H]$^+$,1), 200 (100); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 335.0506. $C_{16}H_{18}{}^{79}BrNO_2$ requires 335.0515.

**(3-Bromo-thiophen-2-ylmethyl)-carbamic acid *tert*-butyl ester 168f**




General procedure **H** was followed using amine hydrochloride **164f** (183 mg, 0.80 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (169 µl, 1.20 mmol) and $Boc_2O$ (192 mg, 0.88 mmol). Flash chromatography (hexane:EtOAc, 20:1–10:1) afforded carbamate **168f** as a colourless solid (164 mg, 70%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.85; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3341 (NH), 2978, 1699 (C=O), 1505, 1167; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.18 (1H, d, *J* 5.4, Het*H*), 6.89 (1H, d, *J* 5.4, Het*H*), 5.12 (1H, br s, N*H*), 4.41 (2H, d, *J* 6.0, C$H_2$), 1.44 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 155.3 (C), 136.3 (C), 129.7 (CH), 124.7 (CH), 109.0 (C), 79.7 (C), 38.5 ($CH_2$), 28.2 (3x$CH_3$); ***m/z*** (EI) 293 ([$^{81Br}$M]$^+$, 1 %), 291 ([$^{79Br}$M]$^+$, 1), 236 (26), 234 (24), 177 (28), 175 (27), 156 (100); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 290.9917. $C_{10}H_{14}{}^{79}BrNO_2S$ requires 290.9923.

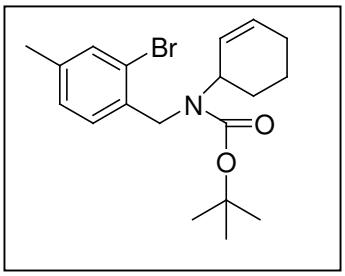
**General procedure J - Dialkylation**

To a suspension of the appropriate amine hydrochloride (1 eq) in MeCN (5 ml) at 0 $^{o}$C was added $^{i}Pr_2NEt$ (4 eq) and the reaction was stirred for 5 mins. 3-Bromocyclohexene (1 eq) was added and the reaction stirred for 16 h at r.t. The reaction was concentrated under reduced pressure and the residue taken up in $CH_2Cl_2$ (5 ml) and washed with NaCl (3 x 5 ml, sat. aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was taken up in $CH_2Cl_2$ (10 ml), $Et_3N$ (1 eq) was added, and the reaction was stirred for 10 mins. The reaction was cooled to 0 $^{o}$C, $Boc_2O$ (1.5 eq) was added and the reaction was stirred for a further 10 mins and then allowed to warm to r.t. and stirred for 16 h. The reaction was diluted with $CH_2Cl_2$ (20 ml), extracted with NaCl (3 x 20 ml, sat. aq.), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography afforded the desired Boc amide.

**General procedure K – Monoalkylation**

To a solution of Boc carbamate (87 mg, 0.23 mmol) in DMF (1.5 ml) at 0 $^{o}$C was added NaH (2 eq, 60% dispersion in mineral oil) and the reaction warmed to r.t. for 40 mins. The reaction was then cooled to 0 $^{o}$C and 3-bromocyclohexene (2 eq) was added dropwise. The reaction allowed to warm to r.t. and stirred for 16 h. $Et_2O$ (10 ml) was added and the organics washed with NaCl (3 x 15 ml, sat. aq.). The organics were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography to afford the desired cyclohexenyl amine.

**2-Bromo-4-methylbenzyl cyclohex-2-enyl-carbamic acid *tert*-butyl ester 165a**

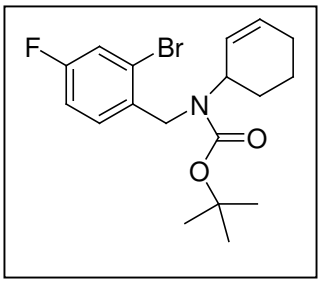



General procedure **J** was followed using amine hydrochloride **164a** (150 mg, 0.63 mmol), MeCN (3 ml), $^{i}Pr_2NEt$ (442 µl, 2.54 mmol), 3-Bromocyclohexene (73 µl, 0.63 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (134 µl, 0.95 mmol) and $Boc_2O$ (208 mg, 0.95 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded Boc amide **165a** as a colourless oil (140 mg, 59%).

General procedure **K** was followed using Boc carbamate **168a** (198 mg, 0.659 mmol), DMF (5 ml), NaH (53 mg, 60% dispersion in mineral oil, 1.32 mmol) and 3-bromocyclohexene (153 µl, 1.32 mmol). Flash chromatography (hexane-hexane:EtOAc, 100:1) afforded cyclohexenyl amine **165a** as a colourless oil (175 mg, 70%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.76; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2978, 2927, 1640 (C=O), 1362, 1190; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.33 (1H, s, Ar*H*), 7.14 (1H, d, *J* 7.9, Ar*H*), 7.07 (1H, d, *J* 7.9, Ar*H*), 5.82-5.80 (1H, m, C*H*=CH), 5.47 (1H, d, *J* 10.2, CH=C*H*), 4.84 (1H, br s, C*H*N), 4.39-4.34 (2H, m, $CH_2$Ar), 2.30 (3H, s, $CH_3$), 2.04-1.84 (3H, m, $CH_2$+$CH_AH_B$), 1.80-1.68 (1H, m, $CH_AH_B$), 1.65-1.25 (11H, m, $CH_2$+3x$CH_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.7 (C), 137.6 (C), 135.9 (C), 132.6 (CH), 131.1 (CH), 128.2 (CH), 127.8 (CH), 127.3 (CH), 121.8 (C), 79.5 (C), 53.0 (CH), 47.3 ($CH_2$), 28.2 (3x$CH_3$), 28.1 ($CH_2$), 24.4 ($CH_2$), 21.3 ($CH_2$), 20.3 ($CH_3$); ***m/z*** (FAB, 3-NOBA) 382 ([$^{81Br}$M+H]$^+$, 12 %), 380 ([$^{79Br}$M+H]$^+$, 15), 326 (100), 324 (100), 185 (96), 183 (97); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 379.1142. $C_{19}H_{26}{}^{79}BrNO_2$ requires 379.1141.

**2-Bromo-4-fluorobenzyl cyclohex-2-enyl-carbamic acid *tert*-butyl ester 165b**

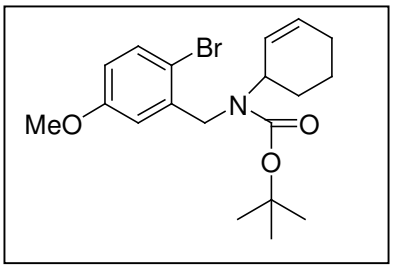



General procedure **J** was followed using amine hydrochloride **164b** (150 mg, 0.62 mmol), MeCN (3 ml), $^{i}Pr_2NEt$ (435 µl, 2.50 mmol), 3-Bromocyclohexene (72 µl, 0.62 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (132 µl, 0.94 mmol) and $Boc_2O$ (205 mg, 0.94 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded Boc amide **165b** as a colourless oil (161 mg, 67%).

General procedure K was followed using Boc carbamate **168b** (175 mg, 0.56 mmol), DMF (4 ml), NaH (46 mg, 60% dispersion in mineral oil, 1.15 mmol) and 3-bromocyclohexene (133 µl, 1.15 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded cyclohexenyl amine **165b** as a colourless oil (157 mg, 71%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.75; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2975, 2932, 1694 (C=O), 1485, 1169; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.29-7.22 (2H, m, 2xAr*H*), 7.01 (1H, dt, *J* 8.4, 2.6, Ar*H*), 5.86-5.84 (1H, m, C*H*=CH), 5.46 (1H, d, *J* 10.2, CH=C*H*), 4.83 (1H, br s, *CHN*), 4.30-4.26 (2H, m, C$H_2$Ar), 2.06-1.85 (3H, m, C$H_2$+C$H_A$H$_B$), 1.79-1.73 (1H, m, CH$_A$$H_B$), 1.70-1.55 (1H, m, C$H_C$H$_D$), 1.55-1.20 (10H, m, CH$_C$$H_D$+3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 161.0 (1C, d, *J* 249.0, C), 155.7 (C), 135.0 (C), 131.4 (CH), 128.5 (CH), 128.0 (CH), 121.7 (1C, d, *J* 9.5, C), 119.4 (1C, d, *J* 24.5, CH), 114.1 (1C, d, *J* 20.9, CH), 79.9 (C), 53.1 (CH), 47.0 ($CH_2$), 28.2 (3x$CH_3$), 28.1 ($CH_2$), 24.5 ($CH_2$), 21.3 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 386 ([$^{81Br}$M+H]$^+$, 86 %), 384 ([$^{79Br}$M+H]$^+$, 95), 330 (98), 328 (98), 301 (47), 299 (49), 284 (96), 282 (97), 250 (96), 248 (97), 246 (94), 204 (77), 202 (87); **HRMS** (FAB, 3-NOBA) Found: [$^{79Br}$M]$^+$, 384.0969. $C_{18}H_{24}{}^{79}BrFNO_2$ requires 384.0969.

**(2-Bromo-5-methoxybenzyl)-(cyclohex-2-enyl)-carbamic acid *tert*-butyl ester 165c**

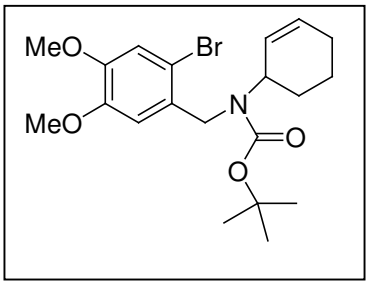



General procedure **J** was followed using amine hydrochloride **164c** (200 mg, 0.79 mmol), MeCN (5 ml), $^{i}Pr_2NEt$ (552 µl, 3.17 mmol), 3-Bromocyclohexene (92 µl, 0.79 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (167 µl, 1.19 mmol) and $Boc_2O$ (260 mg, 1.19 mmol). Flash chromatography (hexane:EtOAc, 100:1–20:1) afforded Boc amide **165c** as a colourless oil (181 mg, 58%).

General procedure **K** was followed using Boc carbamate **168c** (222 mg, 0.703 mmol), DMF (5 ml), NaH (56 mg, 60% dispersion in mineral oil, 1.41 mmol) and 3-bromocyclohexene (163 µl, 1.41 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded cyclohexenyl amine **165c** as a colourless oil (201 mg, 72%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.74; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2975, 2929, 1694 (C=O), 1168; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.45 (1H, d, *J* 8.8, Ar*H*), 6.85 (1H, d, *J* 3.1, Ar*H*), 6.66 (1H, dd, *J* 8.8, 3.1, Ar*H*), 5.89-5.80 (1H, m, C*H*=CH), 5.49 (1H, d, *J* 10.1, CH=C*H*), 4.88 (1H, br s, C*H*N), 4.37 (1H, d, *J* 17.4, $CH_XH_YAr$), 4.30 (1H, d, *J* 17.4, $CH_XH_YAr$), 3.77 (3H, s, $OCH_3$), 2.08-1.87 (3H, m, $CH_2$+$CH_AH_B$), 1.80-1.71 (1H, m, $CH_AH_B$), 1.70-1.29 (11H, m, $CH_2$+3x$CH_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 159.1 (C), 155.7 (C), 132.8 (CH), 131.4 (C), 128.2 (2xCH), 113.8 (CH), 113.4 (CH), 112.5 (C), 79.8 (C), 55.3 ($CH_3$), 53.4 (CH), 47.7 ($CH_2$), 28.3 ($CH_2$), 28.2 (3x$CH_3$), 24.5 ($CH_2$), 21.3 ($CH_2$); ***m/z*** (EI) 398 ([$^{81Br}$M+H]$^+$, 7 %), 396 ([$^{79Br}$M+H]$^+$, 9), 342 (100), 340 (100), 260 (100), 201 (41), 199 (42); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 395.1090. $C_{19}H_{26}{}^{79}BrNO_3$ requires 395.1090.

**2-Bromo-4,5-dimethoxybenzyl-(cyclohex-2-enyl)-carbamic acid *tert*-butyl ester 165d**

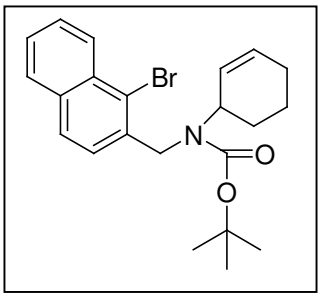



General procedure **J** was followed using amine hydrochloride **164d** (200 mg, 0.710 mmol), MeCN (5 ml), $^{i}Pr_2NEt$ (493 µl, 2.83 mmol), 3-Bromocyclohexene (82 µl, 0.710 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (149 µl, 0.71 mmol) and $Boc_2O$ (927 mg, 4.25 mmol). Flash chromatography (hexane:EtOAc:$Et_3N$, 100:5:0.5) afforded the Boc amide **165d** as a colourless oil (170 mg, 56%).

General procedure **K** was followed using Boc carbamate **168d** (87 mg, 0.23 mmol), DMF (1.5 ml), NaH (18 mg, 60% dispersion in mineral oil, 0.46 mmol) and 3-bromocyclohexene (53 µl, 0.46 mmol). Flash chromatography (hexane:EtOAc:$Et_3N$, 100:5:0.5) afforded cyclohexenyl amine **165d** as a colourless oil (81 mg, 84%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.49; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1640 (C=O), 1362, 1190, 1177; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.97 (1H, s, Ar*H*), 6.82 (1H, s, Ar*H*), 5.85-5.77 (1H, m, C*H*=CH), 5.44 (1H, d, *J* 10.0, CH=C*H*), 4.80 (1H, br s, C*H*N), 4.35 (1H, d, *J* 16.5, C$H_X$H$_Y$Ar), 4.26 (1H, d, *J* 16.5, CH$_X$$H_Y$Ar), 3.83 (3H, s, C$H_3$), 3.81 (3H, s, C$H_3$), 2.05-1.92 (2H, m, C$H_2$), 1.91-1.80 (1H, m, C$H_A$H$_B$), 1.74-1.65 (1H, m, CH$_A$$H_B$), 1.65-1.30 (11H, m, C$H_2$+3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.7 (C), 148.6 (C), 148.3 (C), 131.3 (C), 131.1 (CH), 128.2 (CH), 115.6 (CH), 111.8 (C), 111.2 (CH), 79.6 (C), 56.1 ($CH_3$), 55.9 ($CH_3$), 53.1 (CH), 47.1 ($CH_2$), 28.2 (3x$CH_3$), 28.1 ($CH_2$), 24.4 ($CH_2$), 21.3 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 428 ([$^{81Br}$M+H]$^+$, 6 %), 426 ([$^{79Br}$M+H]$^+$, 9), 372 (34), 370 (40), 346 (16), 326 (10), 290 (100), 231 (100), 229 (100); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 426.1268. $C_{20}H_{29}{}^{79}BrNO_4$ requires 426.1275.

**1-Bromo-naphthalen-2-ylmethyl-(cyclohex-2-enyl)-carbamic acid *tert*-butyl ester 165e**

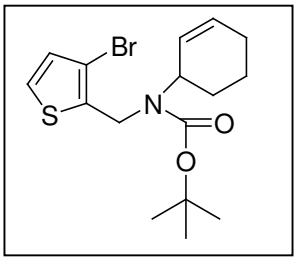



General procedure **J** was followed using amine hydrochloride **164e** (150 mg, 0.55 mmol), MeCN (3 ml), $^{i}Pr_2NEt$ (383 µl, 2.20 mmol), 3-Bromocyclohexene (64 µl, 0.55 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (116 µl, 0.83 mmol) and $Boc_2O$ (180 mg, 0.83 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded the Boc amide **165e** as a colourless oil (140 mg, 61%).

General procedure **K** was followed using Boc carbamate **168e** (165 mg, 0.49 mmol), DMF (5 ml), NaH (40 mg, 60% dispersion in mineral oil, 0.982 mmol) and 3-bromocyclohexene (114 µl, 0.98 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded cyclohexenyl amine **165e** as a colourless oil (175 mg, 86%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.80; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1652 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 8.33 (1H, d, *J* 8.7, Ar*H*), 7.82 (1H, d, *J* 7.4, Ar*H*), 7.80 (1H, d, *J* 8.4, Ar*H*), 7.58 (1H, t, *J* 6.9, Ar*H*), 7.48 (1H, ddd, *J* 8.3, 7.2, 1.1, Ar*H*), 7.43 (1H, d, *J* 8.6, Ar*H*), 5.83 (1H, br s, C*H*=CH), 5.52 (1H, d, *J* 10.0, CH=C*H*), 4.95 (1H, br s, C*H*N), 4.66 (2H, br s, $CH_2$Ar), 2.10-1.88 (3H, m, $CH_2$+$CH_AH_B$), 1.80-1.71 (1H, m, $CH_AH_B$), 1.70-1.30 (11H, m, $CH_2$+3x$CH_3$);**$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.9 (C), 137.3 (C), 133.6 (C), 132.2 (C), 131.3 (CH), 128.2 (CH), 127.9 (CH), 127.2 (2xCH), 126.7 (CH), 125.9 (CH), 125.0 (CH), 121.5 (C), 79.8 (C) 53.0 (CH), 48.6 ($CH_2$), 28.2 (3x$CH_3$), 28.1 ($CH_2$), 24.5 ($CH_2$), 21.3 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 418 ([$^{81Br}$M+H]$^+$, 2 %), 416 ([$^{79Br}$M+H]$^+$, 3), 362 (80), 360 (85), 221 (100), 219 (100), 200 (33), 141 (41), 139 (36); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 415.1140. $C_{22}H_{26}N^{79}BrNO_2$ requires 415.1141.

**(3-Bromo-thiophen-2-ylmethyl)-(cyclohex-2-enyl)-carbamic acid *tert*-butyl ester 165f**

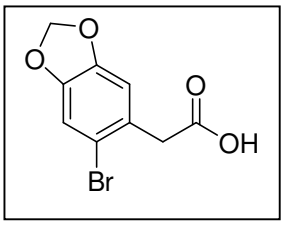



General procedure **J** was followed using amine hydrochloride **164f** (150 mg, 0.66 mmol), MeCN (3 ml), $^{i}Pr_2NEt$ (457 µl, 2.62 mmol), 3-Bromocyclohexene (76 µl, 0.66 mmol), $CH_2Cl_2$ (10 ml), $Et_3N$ (138 µl, 0.98 mmol) and $Boc_2O$ (215 mg, 0.98 mmol). Flash chromatography (hexane:EtOAc, 100:1 – 100:2) afforded Boc amide **165f** as a colourless oil (160 mg, 65%).

General procedure **K** was followed using Boc carbamate **168f** (155 mg, 0.53 mmol), DMF (5 ml), NaH (42 mg, 60% dispersion in mineral oil, 1.06 mmol) and 3-bromocyclohexene (123 µl, 1.06 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded cyclohexenyl amine **165f** as a yellow oil (180 mg, 91%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.85; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1696 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.17 (1H, d, *J* 5.3, Het*H*), 6.87 (1H, d, *J* 5.3, Het*H*), 5.91-5.84 (1H, m, C*H*=CH), 5.49 (1H, dt, *J* 10.2, 1.2, CH=C*H*), 4.74 (1H, s, C*H*N), 4.51-4.41 (2H, m, C$H_2$Ar), 2.16-1.99 (2H, m, C$H_2$), 1.91-1.81 (1H, m, C$H_A$H$_B$), 1.80-1.68 (1H, m, CH$_A$$H_B$), 1.68-1.50 (2H, m, C$H_2$), 1.46 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.3 (C), 139.4 (C), 131.4 (CH), 129.2 (CH), 128.3 (CH), 124.2 (CH), 107.7 (C), 80.2 (C), 53.3 (CH), 42.6 ($CH_2$), 28.3 (3x$CH_3$), 27.4 ($CH_2$), 24.6 ($CH_2$), 21.5 ($CH_2$); ***m/z*** (FAB, 3-NOBA) 374 ([$^{81Br}$M+H]$^+$, 18 %), 372 ([$^{79Br}$M+H]$^+$, 22), 318 (99), 316 (99), 236 (51), 234 (43), 177 (98), 175 (49), 154 (58), 140 (31), 138 (24), 136 (36); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 371.0549. $C_{16}H_{22}{}^{79}BrNO_2S$ requires 371.0549.

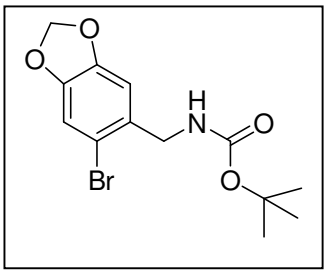
**(6-Bromo-benzo[1,3]dioxol-5-yl)-acetic acid 169k**[196]




To a solution of 1,3-benzodioxole-5-acetic acid (700 mg, 3.89 mmol) and NaOH (1.0 ml, 5 M aq.) in $H_2O$ (7 ml) was added DBDMH (600 mg, 2.10 mmol) and the reaction stirred at r.t. under an air atmosphere for 48 h. The reaction was diluted with $H_2O$ (50 ml), acidified to pH 1 with HCl (6 M, aq.) and extracted into $Et_2O$ (3 x 30 ml). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford acid **169k** as a colourless crystalline powder (909 mg, 91% yield).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.23; **MP** 191 °C (EtOH), lit. 190 °C[196]; **$\upsilon_{max}$** (NUJOL)/$cm^{-1}$ 1699 (C=O); **$^1$H NMR** δ (250 MHz, DMSO) 7.21 (1H, s, Ar*H*), 7.02 (1H, s, Ar*H*), 6.07 (2H, s, OC$H_2$O), 3.63 (2H, s, ArC$H_2$); **$^{13}$C NMR** δ (62.9 MHz, DMSO), 171.4 (C), 147.0 (C), 146.8 (C), 127.9 (C), 114.7 (C), 111.9 (CH), 111.4 (CH), 101.7 ($CH_2$), 40.6 ($CH_2$); ***m/z*** (EI) 260 ([$^{81Br}$M]$^+$, 49 %), 258 ([$^{81Br}$M]$^+$, 48), 215 (97), 213 (100), 179 (92), 135 (38), 113 (27); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 257.9521. $C_9H_7O_4{}^{79}Br$ requires 257.9522.

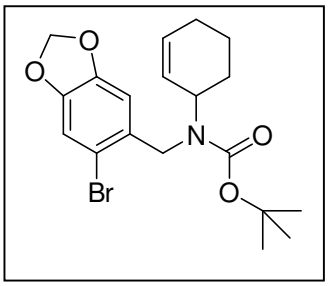
**6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-carbamic acid *tert*-butyl ester 168k**



To a suspension of acid **169k** (1.72 g, 6.64 mmol) and $Et_3N$ (1.31 ml, 9.40 mmol) in $CH_2Cl_2$ (50 ml) at 0 °C was added diphenylphosphoryl azide (2.00 ml, 9.30 mmol) and the reaction stirred at 0 °C for 30 mins. The reaction was warmed to r.t. and stirred for 30 mins before being filtered through a silica gel plug. The crude organics were concentrated under reduced pressure and refluxed in toluene (50 ml) at 80 °C for 1 h. The reaction was concentrated under reduced pressure and then refluxed at 80 °C in $^{t}$BuOH (50 ml) for 19 h. The reaction was concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 100:2–100:8) to afford carbamate **168k** as a colourless oil (1.09 g, 50%).

**$R_f$** [hexane:EtOAc, 10:1] = 0.21; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3346 (NH), 1694 (C=O), 1470; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 6.99 (1H, s, Ar*H*), 6.95 (1H, s, Ar*H*), 5.97 (2H, s, $OCH_2O$), 4.99 (1H, br s, N*H*), 4.28 (2H, d, *J* 6.2, C$H_2$Ar), 1.46 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$), 155.6 (C), 147.4 (C), 147.3 (C), 131.1 (C), 113.6 (C), 112.5 (CH), 109.5 (CH), 101.6 ($CH_2$), 79.4 (C), 44.5 ($CH_2$), 28.2 (3x$CH_3$); ***m/z*** (EI) 331 ([$^{81Br}$M]$^+$, 1 %), 329 ([$^{79Br}$M]$^+$, 1), 274 (1), 272 (1), 194 (7), 49 (100). **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 329.0258. $C_{13}H_{16}O_4N^{79}Br$ requires 329.0257.

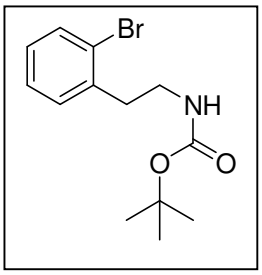
**(4-Bromo-benzo[1,3]dioxol-5-ylmethyl)-(cyclohex-2-enyl)-carbamic acid *tert*-butyl ester 165k**



General procedure **K** was followed using Boc carbamate **168k** (140 mg, 0.42 mmol), DMF (4 ml), NaH (34 mg, 60% dispersion in mineral oil, 0.84 mmol) and 3-bromocyclohexene (100 µl, 0.84 mmol). Flash chromatography (hexane:EtOAc, 100:1–100:3) afforded cyclohexene **165k** as a colourless oil (130 mg, 75%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.69; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1693 (C=O), 1479; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.95 (1H, s, Ar*H*), 6.78 (1H, s, Ar*H*), 5.93 (2H, s, OC$H_2$O), 5.83-5.81 (1H, m, C*H*=CH), 5.45 (1H, br d, *J* 10.2, CH=C*H*), 4.76 (1H, br s, C*H*N), 4.34-4.15 (2H, m, C$H_2$Ar), 2.01-1.97 (2H, m, C$H_2$), 1.90-1.88 (1H, m, C$H_A$H$_B$), 1.75-1.73 (1H, m, CH$_A$$H_B$), 1.63-1.59 (2H, m, C$H_2$), 1.44-1.41 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$), 155.7 (C), 147.4 (C), 146.8 (C), 132.6 (C), 131.0 (CH), 128.2 (CH), 112.3 (CH), 112.0 (C), 107.7 (CH), 101.4 ($CH_2$), 79.8 (C), 53.2 (CH), 47.5 ($CH_2$), 28.3 (3x$CH_3$), 28.0 ($CH_2$), 24.5 ($CH_2$), 21.3 ($CH_2$); ***m/z*** (EI) 411 ([$^{81Br}$M]$^+$, 1 %), 409 ([$^{79Br}$M]$^+$, 1), 274 (92), 215 (65), 213 (69), 194 (100); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 409.0889. $C_{19}H_{24}O_4N^{79}Br$ requires 409.0883.

**2-(2'-Bromophenyl) ethyl-*tert*-butyl ester 184j**

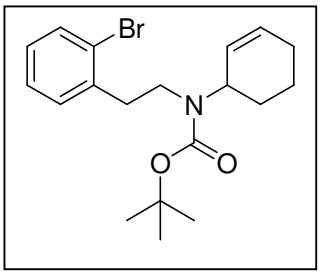



General procedure **H** was followed using amine hydrochloride **164j** (100 mg, 0.42 mmol), $CH_2Cl_2$ (5 ml), $Et_3N$ (89 µl, 0.64 mmol) and $Boc_2O$ (102 mg, 0.47 mmol). Flash chromatography (hexane:EtOAc, 25:1–5:1) afforded carbamate **184j** as a colourless oil (71 mg, 56%).

**Curtius:** To a suspension of 3-(2-bromo-phenyl)-propionic acid (200 mg, 0.87 mmol) and $Et_3N$ (172 µl, 1.22 mmol) in $CH_2Cl_2$ (10 ml) at 0 °C was added diphenylphosphoryl azide (263 µl, 1.22 mmol) and the reaction was stirred at 0 °C for 30 mins. The reaction was warmed to r.t. and stirred for 30 mins before being filtered through a silica gel plug. The crude organics were concentrated under reduced pressure and heated in toluene (10 ml) at 80 °C for 1 h. The reaction was concentrated under reduced pressure and then heated at 80 °C in $^t$BuOH (10 ml) for 19 h. The reaction was concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 25:1–5:1) to afford carbamate **184j** as a colourless oil (201 mg, 77%).

**$R_f$** [3: 1 hexane: EtOAc] = 0.65; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3300 (NH), 2977, 1700 (C=O), 1507, 1472, 1364; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.55 (1H, d, *J* 7.7, Ar*H*), 7.27-7.22 (2H, m, 2xAr*H*), 7.10-7.06 (1H, m, Ar*H*), 4.55 (1H, br s, N*H*), 3.41 (2H, q, *J* 6.7, C$H_2$NH), 2.96 (2H, t, *J* 7.1, C$H_2$Ar), 1.45 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 155.7 (C), 138.4 (C), 132.9 (CH), 130.9 (CH), 128.0 (CH), 127.4 (CH), 124.6 (C), 79.2 (C), 40.4 ($CH_2$), 36.4 ($CH_2$), 28.3 (3x$CH_3$); ***m/z*** (EI) 301 ([$^{81Br}$M]$^+$, 2 %), 299 ([$^{79Br}$M]$^+$, 2), 286 (2), 284 (2), 245 (14), 243 (14), 172 (19), 170 (19), 164 (100); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 299.0512. $C_{13}H_{18}{}^{79}BrNO_2$ requires 299.0515.

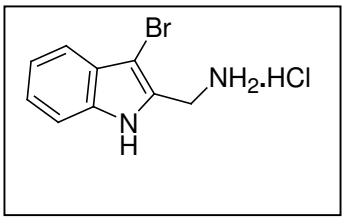
**[2-(2'-Bromophenyl) ethyl]–cyclohex-2-enyl-carbamic acid *tert*-butyl ester 185j**




General procedure **K** was followed using Boc carbamate **184j** (67 mg, 0.223 mmol), DMF (2 ml), NaH (18 mg, 60% dispersion in mineral oil, 0.446 mmol) and 3-bromocyclohexene (52 µl, 0.446 mmol). Flash chromatography (hexane:EtOAc, 100:1–10:1) afforded cyclohexene **185j** as a colourless oil (38 mg, 45%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.79; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2931, 1689 (C=O); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.53 (1H, d, *J* 7.9, Ar*H*), 7.27-7.21 (2H, m, 2xAr*H*), 7.09-7.04 (1H, m, Ar*H*), 5.84-5.82 (1H, m, C*H*=CH), 5.43 (1H, d, *J* 9.7, CH=C*H*), 4.66 (1H, br s, C*H*N), 3.30 (2H, dd, *J* 8.1, 6.2, C$H_2$), 3.04 (2H, m, C$H_2$), 2.10-1.93 (2H, m, C$H_2$), 1.85-1.78 (2H, m, C$H_2$), 1.63-1.58 (2H, m, C$H_2$), 1.52 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 155.7 (C), 139.4 (C), 132.8 (CH), 131.0 (CH), 130.9 (CH), 129.0 (CH), 127.8 (CH), 127.4 (CH), 124.5 (C), 79.4 (C), 53.3 (CH), 44.1 ($CH_2$), 37.0 ($CH_2$), 28.5 (3x$CH_3$), 28.1 ($CH_2$), 24.6 ($CH_2$), 21.6 ($CH_2$); ***m/z*** (EI) 381 ([$^{81Br}$M]$^+$, 2 %), 379 ([$^{79Br}$M]$^+$, 2), 325 (9), 323 (9), 271 (6), 273 (6), 184 (22), 182 (22); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 379.1137. $C_{19}H_{26}{}^{79}BrNO_2$ requires 379.1141.

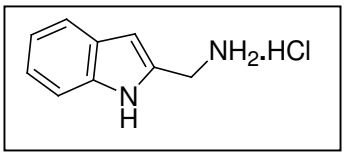
**3-Bromoindole-2-methylamine hydrochloride 164h**




To a suspension of $LiAlH_4$ (587 mg, 15.5 mmol) in THF (20 ml) at 0 $^oC$ was added dropwise a solution of amide **162h** (920 mg, 3.87 mmol) in THF (2 ml). The reaction was allowed to warm to r.t. and then heated at 70 $^oC$ for 18 h. The reaction was quenched by the addition of $Na_2SO_4.5H_2O$ portionwise, then it was filtered and the filtrate stirred vigorously with potassium sodium tartrate (100 ml, sat. aq.) for 1 h. The THF layer was separated and the aqueous phase extracted with $Et_2O$ (3 x 60 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2$ (1 ml), and HCl in $Et_2O$ (20.0 ml, 1 M in $Et_2O$) added. The brown precipitate was filtered and dried to afford a mixture of two products: amine hydrochloride **164h** (528 mg, 52 %) and debrominated amine hydrochloride **191** (118 mg, 17%). The full reduction protocol above was also repeated and crude reaction mixture purified by flash chromatography ($CH_2Cl_2$:MeOH, 9:1) rather than HCl salt formation. This led to the recovery of a minor amount of the free amine of debrominated amine **191**.

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.27; **$^1$H NMR** δ (360 MHz, $CD_3OD$) 7.51 (1H, dt, *J* 7.9, 1.1, Ar*H*), 7.47 (1H, dt, *J* 8.3, 1.1 Ar*H*), 7.29 (1H, ddd, *J* 8.3, 7.2, 1.4, Ar*H*), 7.19 (1H, ddd, *J* 7.9, 7.2, 1.1, Ar*H*), 4.38 (2H, s, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, ($CD_3OD$) 135.5 (C), 126.4 (C), 126.2 (C), 123.2 (CH), 119.9 (CH), 118.1 (CH), 111.1 (CH), 91.9 (C), 33.9 ($CH_2$); ***m/z*** (EI) 226 ([$^{81Br}$M(**164h**)]$^+$, 62 %), 224 ([$^{79Br}$M(**164h**)]$^+$, 64), 209 (91), 207 (86), 146 ([M(**191**]$^+$, 76), 145 (59), 128 (100); **HRMS** (EI) Found: [$^{79Br}$M(**164h**)]$^+$, 223.9947. $C_9H_9{}^{79}BrN_2$ requires 223.9944.

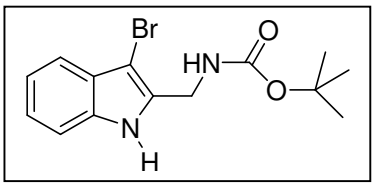
**Data for Indole-2-methylamine hydrochloride 191.**[122]




**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.14; **$^1$H NMR** δ (360 MHz, $CD_3OD$) 7.56 (1H, dt, *J* 7.9, 1.1, Ar*H*), 7.41 (1H, dd, *J* 7.6, 0.7, Ar*H*), 7.17 (1H, ddd, *J* 8.3, 7.2, 1.1, Ar*H*), 7.06 (1H, ddd, *J* 7.9, 7.2, 1.1, Ar*H*), 6.60 (1H, s, =C*H*), 4.32 (2H, s, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, ($CD_3OD$) 121.6 (CH), 119.6 (CH), 118.9 (CH), 110.4 (CH), 101.6 (CH), 35.7 ($CH_2$). **Free amine: $^1$H NMR** δ (250 MHz, $(CD_3)_2SO$) 10.93 (1H, br s, N*H*), 7.44 (1H, dd, *J* 7.1, 1.0, Ar*H*), 7.32 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.03 (1H, td, *J* 7.8, 1.3, Ar*H*), 6.94 (1H, td, *J* 7.1, 1.3, Ar*H*), 6.26 (1H, s, =C*H*), 3.88 (2H, s, C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $(CD_3)_2SO$) 136.1 (C), 128.1 (C), 120.4 (CH), 119.5 (CH), 118.7 (CH), 110.9 (CH), 98.1 (CH), 48.6 ($CH_2$).

$^1$H NMR spectrum in agreement with the literature.[122] $^{13}$C NMR data showed minor discrepancies.

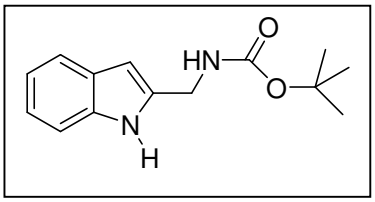
**(3-Bromo-1*H*-indol-2-ylmethyl)-carbamic acid *tert*-butyl ester 168h**



General procedure **H** was followed using 3.06:1 mixture of bromoindole **164h** and debromoindole **191** (130 mg), $CH_2Cl_2$ (6 ml), $Et_3N$ (141 µl, 1.00 mmol) and $Boc_2O$ (218 mg, 1.00 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded bromoindole carbamate **168h** as a yellow oil (87 mg, 49 %) and indole carbamate **192** as a colourless solid (32 mg, 24%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.57; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3401, 2979, 1696 (C=O), 1507, 1165; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 9.20 (1H, br s, N*H*), 7.57 (1H, d, *J* 7.8, Ar*H*), 7.37 (1H, d, *J* 7.6, Ar*H*), 7.30-7.19 (2H, m, 2xAr*H*), 5.19 (1H, br s N*H*), 4.49 (2H, d, *J* 6.2, C$H_2$), 1.54 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, ($CDCl_3$) 157.3 (C), 135.1 (C), 133.8 (C), 126.9 (C), 123.1 (CH), 120.4 (CH), 119.0 (CH), 111.3 (CH), 90.1 (C), 80.4 (C), 36.4 ($CH_2$), 28.3 (3x$CH_3$); ***m/z*** (EI) 326 ([$^{81Br}$M(**168h**)]$^+$, 25 %), 324 ([$^{79Br}$M(**168h**)]$^+$, 25), 270 (25), 268 (26), 246 ([M(**192**)]$^+$, 6), 210 (34), 208 (35), 189 (58), 145 (100); **HRMS** (EI) Found: [$^{79Br}$M(**168h**)]$^+$, 324.0472. $C_{14}H_{17}{}^{79}BrN_2O_2$ requires 324.0468.

**(1*H*-Indol-2-ylmethyl)-carbamic acid *tert*-butyl ester 192 (Diagnostic data)**



**$R_f$** [hexane:EtOAc, 3:1] = 0.48; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 8.77 (1H, br s, N*H*), 7.57 (1H, dd, *J* 7.8, 1.1, Ar*H*), 7.37 (1H, dd, *J* 8.0, 0.9, Ar*H*), 7.18 (1H, td, *J* 7.1, 1.2, Ar*H*), 7.10 (1H, td, *J* 7.9, 1.1, Ar*H*), 6.34 (1H, s, =C*H*), 5.19 (1H, br s N*H*), 4.49 (2H, d, *J* 6.2, C$H_2$), 1.54 (9H, s, 3xC$H_3$).

**Application of optimised methods in Table 3.5 and 3.6**

**9-Methyl phenanthridine 195a-197a**

**(Table 3.5, Entry 2)** General procedure **C** was followed using cyclohexene **165a** (20 mg, 53 µmol), palladacycle **100** (3 mg, 2.6 µmol) and $Ag_2CO_3$ (15 mg, 5.3 µmol). After 2 h at 140 $^oC$, flash chromatography (hexane:EtOAc, 100:1-100:2) afforded the phenanthridine as a colourless solid (18 mg, 99%). $^1H$ NMR of this oil showed it to be a 78: 17: 5 mixture of double bond isomers (**195a**:**196a**:**197a**).

**(Table 3.6, Entry 2)** General procedure **D** was followed using cyclohexene **165a** (110 mg, 0.289 mmol), palladacycle **100** (14 mg, 14.5 µmol) and $MeNCy_2$ (245 µl, 1.16 mmol). After 12 h at 140 $^oC$, flash chromatography (hexane:EtOAc, 100:1-100:2) afforded the phenanthridine as a colourless solid (65 mg, 76%). $^1H$ NMR of this oil showed it to be 26: 57: 11 mixture of double bond isomers (**195a**:**196a**:**197a**).

**9-Fluoro phenanthridine 195b-197b**

**(Table 3.5, Entry 3)** General procedure **C** was followed using cyclohexene **165b** (20 mg, 0.052 mmol), palladacycle **100** (2.5 mg, 2.6 µmol) and $Ag_2CO_3$ (14.5 mg, 0.052 mmol). After 2.5 h at 140 $^oC$, flash chromatography (hexane:EtOAc, 100:1-10:1) afforded the phenanthridine as a colourless oil (16 mg, 99%). $^1H$ NMR of this oil showed it to be an 81: 14: 5 mixture of double bond isomers. (**195b**:**196b**:**197b**).

**(Table 3.6, Entry 3)** General procedure **D** was followed using cyclohexene **165b** (80 mg, 0.21 mmol), palladacycle **100** (10 mg, 10 µmol) and $MeNCy_2$ (175 µl, 0.84 mmol). After 5 h at 140 $^oC$, flash chromatography (hexane:EtOAc, 100:1-100:6) afforded the phenanthridine as a colourless oil (46 mg, 72%). $^1H$ NMR of this oil showed it to be a 27: 44: 29 mixture of double bond isomers **(195b:196b:197b)**.

**8-Methoxy phenanthridine 195c-197c**

**(Table 3.5, Entry 4)** General procedure **C** was followed using cyclohexene **165c** (23 mg, 0.058 mmol), palladacycle **100** (3 mg, 2.9 µmol) and $Ag_2CO_3$ (16 mg, 0.058 mmol). After 4 h at 140 $^oC$, flash chromatography (hexane: EtOAc 100: 1) afforded the phenanthridine as a colourless oil (18 mg, 99%). $^1H$ NMR of this oil showed it to be a 77: 19: 4 mixture of double bond isomers (**195c**:**196c**:**197c**).

(**Table 3.6, Entry 4**) General procedure **D** was followed using cyclohexene **165c** (110 mg, 0.278 mmol), palladacycle **100** (13 mg, 14.0 µmol) and $MeNCy_2$ (236 µl, 1.11 mmol). After 6 h at 140 $^oC$, flash chromatography (hexane:EtOAc, 100:1) afforded the phenanthridine as a colourless oil (64 mg, 73%). $^1H$ NMR of this oil showed it to be a 36: 44: 20 mixture of double bond isomers (**195c**:**196c**:**197c**).

**8,9-Dimethoxy phenanthridine 195d-197d**

**(Table 3.5, Entry 5)** General procedure **C** was followed using cyclohexene **165d** (50 mg, 0.12 mmol), palladacycle **100** (6 mg, 5.9 µmol) and $Ag_2CO_3$ (33 mg, 0.12 mmol). After 1 h at 140 $^oC$, flash chromatography (hexane:EtOAc, 100:15) afforded the phenanthridine as a colourless oil (40 mg, 99%). $^1H$ NMR of this oil showed it to be an 84: 13: 3 mixture of double bond isomers (**195d**:**196d**:**197d**).

(**Table 3.6, Entry 5**) General procedure **D** was followed using cyclohexene **165d** (50 mg, 0.12 mmol), palladacycle **100** (6 mg, 5.9 µmol) and $MeNCy_2$ (100 µl, 0.47 mmol). After 12 h at 140 $^oC$, flash chromatography (hexane:EtOAc, 100:5–100:15) afforded the phenanthridine as a colourless oil (30 mg, 75%). $^1H$ NMR of this oil showed it to be a 41: 32: 27 mixture of double bond isomers (**195d**:**196d**:**197d**).

**Benzo[*k*]phenanthridine 195e-197e**

**(Table 3.5, Entry 6)** General procedure **C** was followed using cyclohexene **165e** (20 mg, 0.05 mmol), palladacycle **100** (2.3 mg, 2.4 µmol) and $Ag_2CO_3$ (14 mg, 0.05 mmol). After 4 h at 140 °C, flash chromatography (hexane: EtOAc 100:2 – 100: 4) afforded the phenanthridine as a colourless oil (14 mg, 88%). $^1$H NMR of this oil showed it to be an 81: 14: 5 mixture of double bond isomers (**195e**:**196e**:**197e**).

(**Table 3.6, Entry 6**) General procedure **D** was followed using cyclohexene **165e** (110 mg, 0.26 mmol), palladacycle **100** (13 mg, 13 µmol) and $MeNCy_2$ (224 µl, 1.06 mmol). After 5 h at 140 °C, flash chromatography (hexane:EtOAc, 100:2–100:3) afforded the phenanthridine as a colourless oil (65 mg, 74%). $^1$H NMR of this oil showed it to be a 44: 42: 16 mixture of double bond isomers (**195e**:**196e**:**197e**).

**Thieno[2,3-*c*]quinoline 195f-197f**

**(Table 3.5, Entry 7)** General procedure **C** was followed using cyclohexene **165f** (20 mg, 0.054 mmol), palladacycle **100** (3 mg, 2.7 µmol) and $Ag_2CO_3$ (15 mg, 0.054 mmol). After 3 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1–100:5) afforded the phenanthridine as a colourless oil (15 mg, 99%). $^1$H NMR of this oil showed it to be a 64:21:15 mixture of double bond isomers (**195f**:**196f**:**197f**), with unquantifiable possible traces of the corresponding *trans*-ring junction diastereomers.

(**Table 3.6, Entry 7**) General procedure **D** was followed using cyclohexene **165f** (85 mg, 0.23 mmol), palladacycle **100** (11 mg, 11.4 µmol) and $MeNCy_2$ (194 µl, 0.913 mmol). After 5 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1) afforded the phenanthridine as a colourless oil (52 mg, 79%). $^1$H NMR of this oil showed it to be a 18:34:30 mixture of double bond isomers (**195f**:**196f**:**197f**), with possible traces of the corresponding *trans*-ring junction diastereomers (7:11:0).

**[1,3]dioxolo[4,5-*j*]phenanthridine 195k-197k**

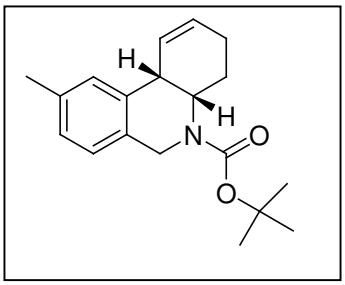
**(Table 3.5, Entry 8)** General procedure **C** was followed using cyclohexene **165k** (65 mg, 0.16 mmol), palladacycle **100** (8 mg, 8 µmol), $Ag_2CO_3$ (44 mg, 0.16 mmol) and DMF (2.5 ml). After 2 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1–100:5) afforded the phenanthridine as a colourless oil (47 mg, 91%). $^1$H NMR of this oil showed it to be an 76:18:6 mixture of double bond isomers (**195k**:**196k**:**197k**).

(**Table 3.6, Entry 8**) General procedure **D** was followed using cyclohexene **165k** (24 mg, 59 µmol), palladacycle **100** (3 mg, 3.0 µmol), $MeNCy_2$ (52 µl, 0.24 mmol) and DMF (2 ml). After 24 h at 140 °C, flash chromatography (hexane:EtOAc, 20:1) afforded the phenanthridine as a colourless oil (12 mg, 59%). $^1$H NMR of this oil showed it to be a 41:26:33 mixture of double bond isomers (**195k**:**196k**:**197k**). Additionally, 32% of the dehalogenated product **198k** was recovered.

**(Table 3.6, Entry 9)** General procedure **E** (Method **A**) was followed using cyclohexene **165k** (85 mg, 0.21 mmol), $Pd_2(dba)_3$ (9.6 mg, 11 µmol), $P(^tBu)_3HBF_4$ (6.1 mg, 21 µmol) and $MeNCy_2$ (176 µl, 0.83 mmol). After 18 h at r.t., flash chromatography (hexane:EtOAc, 100:4) afforded the phenanthridine as a colourless oil (55 mg, 80%). $^1$H NMR of this oil showed it to be a 18:46:36 mixture of double bond isomers (**195k**:**196k**:**197k**). Additionally, 11% of the dehalogenated product **198k** was recovered.

**(Table 3.6, Entry 10)** General procedure **E** (Method **B**) was followed using cyclohexene **165k** (844 mg, 2.06 mmol), $Pd_2(dba)_3$ (94 mg, 0.10 mmol), $P(^tBu)_3HBF_4$ (56 mg, 0.21 mmol) and $MeNCy_2$ (1.75 ml, 8.24 mmol). After 18 h at 50 °C, flash chromatography (hexane:EtOAc, 100:4) afforded the phenanthridine as a colourless oil (676 mg, 99%). $^1$H NMR of this oil showed it to be a 37:39:24 mixture of double bond isomers (**195k**:**196k**:**197k**).

**(4a*SR*,10b*SR*)-9-Methyl-4,4a,6,10b-tetrahydro-3*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 195a ($\Delta^{1,2}$ isomer)**



**$R_f$** [hexane:EtOAc, 10:1] = 0.46; **MP** 105 °C; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2972, 1692 (C=O), 1398, 1364, 1169; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.11 (1H, d, Ar*H*), 7.00 (2H, m, 2xAr*H*), 6.18-6.12 (1H, m, CHC*H*=CH), 5.88-5.83 (1H, m, CH=C*H*$CH_2$), 4.68 (1H, d, *J* 16.3, C$H_X$$H_Y$Ar), 4.41 (1H, br s, NC*H*CH), 4.35 (1H, d, *J* 16.3, C$H_X$$H_Y$Ar), 3.54 (1H, br s, NCHC*H*), 2.34 (3H, s, C$H_3$), 2.29-2.16 (1H, m, C$H_A$$H_B$), 2.15-2.05 (1H, m, C$H_A$$H_B$), 1.74-1.69 (1H, m, C$H_C$$H_D$), 1.61-1.50 (10H, m, 3 x C$H_3$+C$H_C$$H_D$); **$^{13}$C NMR** δ (90.0 MHz, 323 K, $CDCl_3$) 155.0 (C), 137.6 (C), 136.3 (C), 128.2 (CH), 128.1 (CH), 127.4 (CH), 126.6 (CH), 125.9 (CH), 123.8 (C), 79.6 (CH), 50.5 (CH), 43.3 ($CH_2$), 37.2 (CH), 28.5 ($CH_2$), 28.5 (3x$CH_3$), 25.3 ($CH_2$), 21.1 ($CH_3$); ***m/z*** (EI) 299 ($[M]^+$, 1 %), 242 (100), 198 (15), 189 (26), 144 (11); **HRMS** (EI) Found: $[M]^+$ 299.1880. $C_{19}H_{25}NO_2$ requires 299.1880.

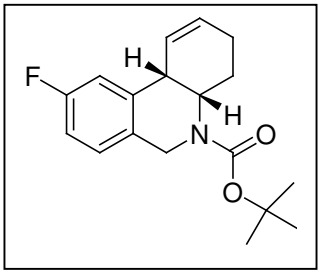
**Diagnostic $^1$H NMR data for 196a ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.04 (3H, m, 3xAr*H*), 5.70-5.66 (1H, m, C*H*=CH), 5.45-5.40 (1H, m, CH=C*H*), 4.55 (1H, d, *J* 16.2, C$H_X$$H_Y$), 4.48 (1H, d, *J* 16.2, C$H_X$$H_Y$), 4.43 (1H, br s, NC*H*), 3.18 (1H, br s, NCHC*H*), 2.86 (1H, dd, *J* 18.1, 4.9, C$H_A$$H_B$), 2.63-2.56 (1H, m, C$H_A$$H_B$), 2.35 (3H, s, C$H_3$), 2.24-2.19 (1H, m, C$H_C$$H_D$), 1.57-1.48 (10H, m, C$H_C$$H_D$+3xC$H_3$).

**Diagnostic $^1$H NMR data for 197a ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$); 5.70-5.68 (1H, m, C*H*=CH), 5.53 (1H, dd, *J* 8.5, CH=C*H*), 5.06 (1H, br s, NC*H*), 4.82 (1H, d, *J* 16.7, C$H_X$$H_Y$), 4.21 (1H, d, *J* 16.7, C$H_X$$H_Y$), 3.26 (1H, br s, NCHC*H*), 2.10-1.95 (1H, m, C$H_A$$H_B$), 1.89-1.79 (1H, m, C$H_A$$H_B$).

**(4a*SR*,10b*SR*)-9-Fluoro-4,4a,6,10b-tetrahydro-3*H*-phenanthridine-5-carboxylic acid tert-butyl ester 195b ($\Delta^{1,2}$ isomer)**




**$R_f$** [hexane:EtOAc, 3:1] = 0.57; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2974, 2928, 1692 (C=O), 1498, 1400, 1365; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.07 (1H, dd, *J* 8.4, 5.7, Ar*H*), 7.00 (1H, dd, *J* 9.9, 2.6, Ar*H*), 6.88 (1H, td, *J* 8.4, 2.6, Ar*H*), 6.12-6.06 (1H, m, CHC*H*=CH), 5.89-5.87 (1H, m, CH=C*H*$CH_2$), 4.65 (1H, d, *J* 16.3, C$H_X$$H_Y$Ar), 4.40 (1H, br s, NC*H*CH), 4.36 (1H, d, *J* 16.3, C$H_X$$H_Y$Ar), 3.53 (1H, br s, NCHC*H*), 2.31-2.18 (1H, m, C$H_A$$H_B$), 2.17-2.08 (1H, m, C$H_A$$H_B$), 1.77-1.68 (1H, m, C$H_C$$H_D$), 1.53-1.46 (10H, m, 3xC$H_3$+C$H_C$$H_D$); **$^{13}$C NMR** δ (90.0 MHz, 323 K, $CDCl_3$) 161.9 (1C, d, *J* 244.1, C), 154.6 (C), 140.0 (1C, d, *J* 6.8, C), 129.0 (CH), 127.5 (1C, d, *J* 8.0, CH), 126.5 (CH), 123.4 (C), 114.4 (1C, d, *J* 22.1, CH), 113.0 (1C, d, *J* 21.8, CH), 79.8 (C), 50.2 (CH), 43.0 ($CH_2$), 37.3 (CH), 28.5 (3x$CH_3$), 25.4 ($CH_2$), 24.0 ($CH_2$); ***m/z*** (EI) 303 ([M]$^+$, 8 %), 247 (95), 246 (90), 202 (27), 193 (100), 148 (36); **HRMS** (EI) Found: [M]$^+$ 303.1626. $C_{18}H_{22}FNO_2$ requires 303.1629.

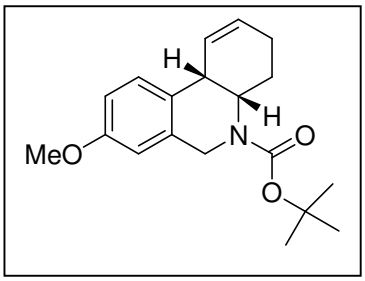
**Diagnostic $^1$H NMR data for 196b ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.12 (1H, dd, *J* 8.3, 5.7, Ar*H*), 6.94 (1H, d, *J* 10.5, Ar*H*), 6.92-6.87 (1H, m, Ar*H*), 5.69-5.66 (1H, m, C*H*=CH), 5.46-5.41 (1H, m, CH=C*H*), 4.57 (1H, d, *J* 16.2, C$H_X$$H_Y$), 4.46 (1H, br s, NC*H*), 4.45 (1H, d, *J* 16.1, C$H_X$$H_Y$), 3.18 (1H, s, NCHC*H*), 2.79-2.73 (1H, m, C$H_A$$H_B$), 2.67-2.60 (1H, m, C$H_A$$H_B$), 2.27-2.20 (1H, m, C$H_C$$H_D$), 1.53-1.45 (10H, m, C$H_C$$H_D$+3xC$H_3$)

**Diagnostic $^1$H NMR data for 197b ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$); 5.69-5.66 (1H, m, C*H*=CH), 5.52 (1H, dd, *J* 10.2, 1.0, CH=C*H*), 5.08 (1H, br s, NC*H*), 4.84 (1H, d, *J* 16.4, C$H_X$$H_Y$), 4.19 (1H, d, *J* 16.4, C$H_X$$H_Y$), 3.28 (1H, br s, NCHC*H*), 2.40-2.30 (1H, m, C$H_A$$H_B$), 2.12-2.00 (1H, m, C$H_A$$H_B$).

**(4a*SR*,10b*SR*)-8-Methoxy-4,4a,6,10b-tetrahydro-3*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 195c ($\Delta^{1,2}$ isomer)**




**$R_f$** [hexane:EtOAc, 3:1] = 0.71; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2974, 1691 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.19 (1H, d, *J* 8.5, Ar*H*), 6.79 (1H, dd, *J* 8.5, 2.7, Ar*H*), 6.66 (1H, d, *J* 2.7, Ar*H*), 6.14-6.09 (1H, m, CHC*H*=CH), 5.84-5.80 (1H, m, CH=C*H*$CH_2$), 4.69 (1H, d, *J* 16.6, C$H_X$$H_Y$Ar), 4.34 (1H, br s, NC*H*CH), 4.30 (1H, d, *J* 16.6, C$H_X$$H_Y$Ar), 3.79 (3H, s, C$H_3$), 3.51 (1H, br s, NCHC*H*), 2.27-2.16 (1H, m, C$H_A$$H_B$), 2.12-2.04 (1H, m, C$H_A$$H_B$), 1.74-1.65 (1H, m, C$H_C$$H_D$), 1.58-1.47 (10H, m, C$H_C$$H_D$+3 x C$H_3$); **$^{13}$C NMR** δ (90.0 MHz, 323 K, $CDCl_3$) 157.9 (C), 154.9 (C), 130.0 (C), 128.5 (CH), 128.0 (CH), 127.6 (CH), 125.4 (CH), 113.0 (CH), 111.1 (CH), 79.6 (C), 55.2 ($CH_3$), 50.5 (CH), 43.7 ($CH_2$), 36.6 (CH), 28.6 (3x$CH_3$), 26.5 ($CH_2$), 25.3 ($CH_2$); ***m/z*** (EI) 315 ($[M]^+$, 2 %), 259 (77), 242 (100), 205 (47); **HRMS** (EI) Found: $[M]^+$ 315.1831. $C_{29}H_{25}NO_3$ requires 315.1829.

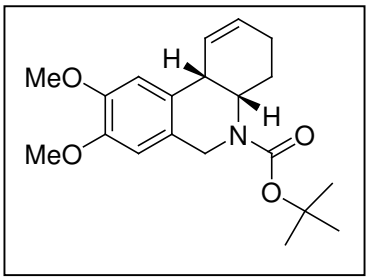
**Diagnostic $^1$H NMR data for 196c ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.14 (1H, d, *J* 8.6, Ar*H*), 6.73 (1H, d, *J* 2.3, Ar*H*), 5.70-5.62 (1H, m, C*H*=CH), 5.44-5.40 (1H, m, CH=C*H*), 4.52 (2H, s, C$H_2$Ar), 3.15 (1H, br s, NCHC*H*), 2.81 (1H, dd, *J* 22.9, 4.7, C$H_A$$H_B$), 2.62-2.54 (1H, m, CH$_A$$H_B$).

**Diagnostic $^1$H NMR data for 197c ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.26 (1H, d, *J* 8.6, Ar*H*), 6.60 (1H, s, Ar*H*), 5.51 (1H, d, *J* 10.2, C*H*=CH), 5.05 (1H, br s, NC*H*), 4.83 (1H, d, *J* 17.1, C$H_X$$H_Y$), 4.22 (1H, d, *J* 17.1, CH$_X$$H_Y$), 3.24 (1H, br s, NCHC*H*).

**(4a*SR*,10b*SR*)-8,9-Dimethoxy-4,4a,6,10b-tetrahydro-3*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 195d ($\Delta^{1,2}$ isomer)**




**$R_f$** [hexane:EtOAc, 3:1] = 0.44; **MP** 124 $^{o}$C; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 2973, 1692 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.77 (1H, s, Ar*H*), 6.60 (1H, s, Ar*H*), 6.12-6.07 (1H, m, CHC*H*=CH), 5.84-5.81 (1H, m, CH=C*H*CH$_2$), 4.62 (1H, d, *J* 16.3, C$H_X$H$_Y$Ar), 4.37 (1H, br s, NC*H*CH), 4.27 (1H, d, *J* 16.3, CH$_X$$H_Y$Ar), 3.85 (3H, s, C$H_3$), 3.83 (3H, s, C$H_3$), 3.47 (1H, br s, NCHC*H*), 2.25-2.20 (1H, m, C$H_A$H$_B$), 2.11-2.03 (1H, m, CH$_A$$H_B$), 1.69-1.65 (1H, m, C$H_C$H$_D$), 1.57 (1H, td, *J* 16.8, 5.8, CH$_C$$H_D$), 1.50-1.48 (9H, m, 3 x C$H_3$); **$^{13}$C NMR** δ (90.0 MHz, 323 K, $CDCl_3$) 155.0 (C), 148.2 (C), 147.6 (C), 129.8 (C), 128.3 (CH), 127.2 (CH), 124.4 (C), 111.2 (CH), 109.5 (CH), 79.7 (C), 56.0 (2xCH$_3$), 50.2 (CH), 43.0 (CH$_2$), 36.6 (CH), 28.4 (3xCH$_3$), 25.3 (CH$_2$), 23.9 (CH$_2$); ***m/z*** (FAB, 3-NOBA) 346 ([M+H]$^+$, 26 %), 289 (100), 244 (82), 216 (36), 190 (52), ; **HRMS** (FAB, 3-NOBA) Found: [M+H]$^+$ 346.2017. $C_{20}H_{28}NO_4$ requires 346.2013.

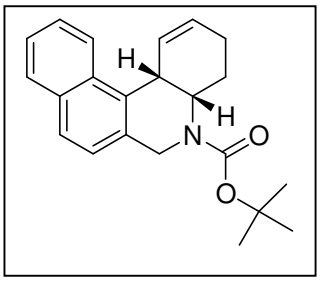
**Diagnostic $^1$H NMR data for 196d ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.75 (1H, s, Ar*H*), 6.66 (1H, s, Ar*H*), 5.67-5.63 (1H, m, C*H*=CH), 5.44-5.40 (1H, m, CH=C*H*), 4.46 (2H, s, C$H_2$Ar), 3.13 (1H, br s, NCHC*H*), 2.77-2.73 (1H, m, C$H_A$H$_B$), 2.61-2.56 (1H, m, CH$_A$$H_B$).

**Diagnostic $^1$H NMR data for 197d ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$); 6.82 (1H, s, Ar*H*), 6.53 (1H, s, Ar*H*), 5.72-5.66 (1H, m, C*H*=CH), 5.48 (1H, dd, *J* 10.1, CH=C*H*), 5.03 (1H, br s, NC*H*), 4.75 (1H, d, *J* 16.5, C$H_X$H$_Y$), 4.13 (1H, d, *J* 16.5, CH$_X$$H_Y$), 3.21 (1H, br s, NCHC*H*).

**(4a*SR*,12c*SR*)-4,4a,6,12c-Tetrahydro-3*H*-benzo[*k*]phenanthridine-5-carboxylic acid *tert*-butyl ester 195e ($\Delta^{1,2}$ isomer)**



**$R_f$** [hexane:EtOAc, 3:1] = 0.80; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2926, 1688 (C=O), 1400, 1166; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 8.08 (1H, d, *J* 8.4, Ar*H*), 7.87 (1H, dd, *J* 8.1, 0.7, Ar*H*), 7.71 (1H, d, *J* 8.3, Ar*H*), 7.55 (1H, ddd, *J* 8.3, 6.8, 1.4, Ar*H*), 7.48 (1H, ddd, *J* 8.1, 6.8, 1.3, Ar*H*), 7.29 (1H, d, *J* 8.3, Ar*H*), 5.97-5.92 (1H, m, C*H*=CH), 5.43 (1H, ddd, *J* 9.9, 1.6, 0.8, CH=C*H*), 5.11 (1H, d, *J* 15.1, $CH_XH_YAr$), 4.62-4.59 (1H, m, C*H*CH=CH), 4.29-4.26 (1H, m, NC*H*), 4.23 (1H, d, *J* 15.1, $CH_XH_YAr$), 2.56-2.21 (1H, m, $CH_CH_D$), 2.37-2.25 (1H, m, $CH_AH_B$), 2.17-2.07 (1H, m, $CH_AH_B$), 1.91-1.84 (1H, dddd, *J* 13.6, 11.3, 5.2, 2.5, $CH_CH_D$), 1.49 (9H, m, 3x$CH_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.2 (C), 133.7 (C), 133.4 (C), 130.6 (2xC), 129.2 (CH), 129.0 (CH), 126.8 (CH), 126.6 (CH), 126.2 (CH), 125.1 (CH), 124.7 (CH), 122.4 (CH), 79.6 (C) 49.8 (CH), 45.2 ($CH_2$), 35.2 (CH), 28.5 (3x$CH_3$), 26.9 ($CH_2$), 20.6 ($CH_2$); ***m/z*** (EI) 335 ($[M]^+$, 4 %), 307 (30), 242 (35), 136 (100); **HRMS** (EI) Found: $[M]^+$,335.1880. $C_{22}H_{25}NNO_2$ requires 335.1880.

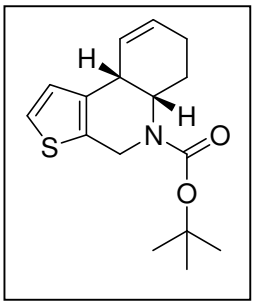
**Diagnostic data for 196e ($\Delta^{2,3}$ isomer).**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 4.98 (1H, d, *J* 16.1, $CH_XH_YAr$), 4.56 (1H, d, *J* 16.1, $CH_XH_YAr$), 4.11 (1H, td, *J* 5.7, 2.6, C*H*$CH_2$), 3.95-3.88 (1H, m, NC*H*$CH_2$), 2.97-2.92 (1H, m, $CH_AH_B$).

**Diagnostic data for 197e ($\Delta^{3,4}$ isomer).**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 4.96 (1H, d, *J* 16.0, $CH_XH_YAr$), 4.81-4.76 (1H, m, C*H*CH=CH), 4.35 (1H, d, *J* 16.0, $CH_XH_YAr$), 4.03-3.97 (1H, m, NC*H*$CH_2$).

**(5a*SR*,9a*SR*)-5a,6,7,9a-Tetrahydro-4*H*-thieno[2,3-*c*]quinoline-5-carboxylic acid *tert*-butyl ester 195f ($\Delta^{1,2}$ isomer)**



**$R_f$** [hexane:EtOAc, 3:1] = 0.79; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3361, 2974, 2928, 1692 (C=O), 1400, 1365; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.16 (1H, d, *J* 5.1, Het*H*), 6.90 (1H, d, *J* 5.1, Het*H*), 6.09-6.05 (1H, m, C*H*=CH), 5.80-5.76 (1H, m, CH=C*H*), 4.98 (1H, d, *J* 16.8, C$H_X$H$_Y$Ar), 4.60 (1H, br s, C*H*N), 4.24 (1H, d, *J* 16.8, 2.0, CH$_X$$H_Y$Ar), 3.48 (1H, br s, NCHC*H*), 2.33-2.20 (1H, m, C$H_A$H$_B$), 2.15-2.06 (1H, m, CH$_A$$H_B$), 1.75-1.60 (2H, m, C$H_2$), 1.51 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.7 (C), 129.5 (C), 127.6 (CH), 127.3 (CH), 125.8 (CH), 123.9 (C), 123.1 (CH), 80.0 (C), 49.3 (CH), 39.9 ($CH_2$), 35.9 (CH), 28.4 (3x$CH_3$), 25.5 ($CH_2$), 22.9 ($CH_2$); ***m/z*** (EI) 292 ($[M+H]^+$, 3 %), 236 (100), 234 (55), 177 (31), 175 (30); **HRMS** (EI) Found: $[M]^+$ 291.1298. $C_{16}H_{21}O_2NS$ requires 291.1288.

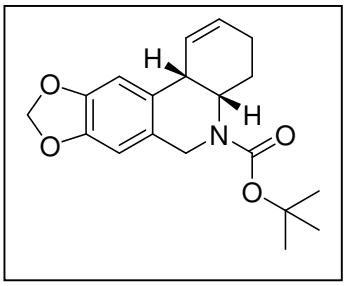
**Diagnostic $^1$H NMR data for 196f ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 5.65-5.58 (1H, m, C*H*=CH), 5.52-5.45 (1H, m, CH=C*H*), 4.89 (1H, d, *J* 17.6, C$H_X$H$_Y$Ar), 4.40 (1H, d, *J* 17.2, CH$_X$$H_Y$Ar), 3.17 (1H, br s, NCHC*H*), 2.72-2.65 (2H, m C$H_2$).

**Diagnostic $^1$H NMR data for 197f ($\Delta^{3,4}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 5.90-5.81 (1H, m, C*H*=CH), 5.50-5.42 (1H, m, CH=C*H*), 4.88 (1H, d, *J* 17.3, C$H_X$H$_Y$Ar), 4.18 (1H, d, *J* 17.3, CH$_X$$H_Y$Ar), 3.24 (1H, br s, NCHC*H*).

**(4a*SR*,11b*SR*)-4,4a,6,11b-Tetrahydro-3*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid *tert*-butyl ester 195k ($\Delta^{1,2}$ isomer)**



**$R_f$** [hexane:EtOAc, 3:1] = 0.65; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1692 (C=O), 1484, 1166; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.77 (1H, s, Ar*H*), 6.59 (1H, s, Ar*H*), 6.08-6.03 (1H, m, C*H*=CH), 5.92 (2H, s, OC$H_2$O), 5.86-5.83 (1H, m, CH=C*H*), 4.58 (1H, d, *J* 16.2, C$H_X$$H_Y$Ar), 4.36 (1H, br s, C*H*CH=CH), 4.29 (1H, d, *J* 16.2, CH$_X$$H_Y$*Ar*), 3.46 (1H, m, NC*H*), 2.26-2.19 (1H, m, C$H_A$H$_B$), 2.16-2.12 (1H, m, CH$_A$$H_B$), 2.72-1.68 (1H, m, C$H_C$H$_D$), 1.60-1.55 (1H, m, CH$_C$$H_D$), 1.51 (1H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.9 (C), 146.7 (C), 145.8 (C), 131.0 (C), 128.5 (CH), 127.2 (CH), 125.7 (C), 107.7 (CH), 106.2 (CH), 100.7 ($CH_2$), 79.6 (C), 50.4 (CH), 43.6 ($CH_2$), 37.1 (CH), 28.5 (3x$CH_3$), 25.3 ($CH_2$), 24.1 ($CH_2$); ***m/z*** (EI) 329 ($[M]^+$, 1 %), 272 (100); **HRMS** (EI) Found: $[M]^+$, 329.1621. $C_{19}H_{23}O_4N$ requires 329.1622.

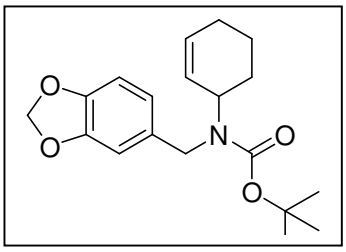
**Diagnostic $^1$H NMR data for 196k ($\Delta^{2,3}$ isomer)**

**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.74 (1H, s, Ar*H*), 6.65 (1H, s, Ar*H*), 5.92 (2H, s, OC$H_2$O), 5.69-5.65 (1H, m, C*H*=CH), 5.47-5.42 (1H, m, CH=C*H*), 4.41 (2H, s, C$H_2$Ar), 3.10 (1H, br s, NCHC*H*), 2.72 (1H, dd, *J* 18.3, 4.9, C$H_A$H$_B$), 2.63-2.56 (1H, m, CH$_A$$H_B$), 2.25-2.20 (1H, m, C$H_C$H$_D$), 1.63-1.55 (1H, m, CH$_C$$H_D$), 1.52 (9H, s, 3xC$H_3$).

**Diagnostic $^1$H NMR data for 197k ($\Delta^{3,4}$ isomer)**

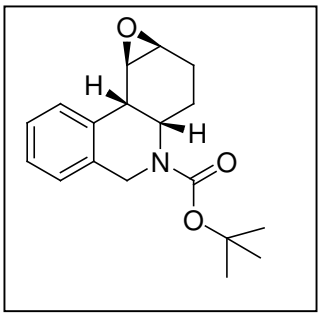
**$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.82 (1H, s, Ar*H*), 6.52 (1H, s, Ar*H*), 5.90 (2H, s, OC$H_2$O), 5.73-5.70 (1H, m, C*H*=CH), 5.52-5.48 (1H, m, CH=C*H*), 5.02 (1H, m, NC*H*), 4.74 (1H, d, *J* 16.5, ArC$H_X$H$_Y$), 4.13 (1H, d, *J* 16.5, ArCH$_X$$H_Y$), 3.20 (1H, m, NCHC*H*).

**(Benzo[1,3]dioxol-5-ylmethyl)-(cyclohex-2-enyl)-carbamic acid *tert*-butyl ester 198k**



**$R_f$** [hexane:EtOAc, 3:1] = 0.69; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 1686 (C=O), 1490, 1245, 1166; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.77 (1H, br s, Ar*H*), 6.73 (1H, d, *J* 8.0, Ar*H*), 6.69 (1H, br d, *J* 8.6, Ar*H*), 5.93 (2H, s, O$CH_2$O), 5.82-5.80 (1H, m, C*H*=CH), 5.49 (1H, d, *J* 10.2, CH=C*H*), 4.71 (1H, br s, C*H*N), 4.34 (1H, d, *J* 16.0, $CH_XH_Y$Ar), 4.20 (1H, d, *J* 16.0, $CH_XH_Y$Ar), 1.99-1.97 (2H, m, $CH_2$), 1.90-1.82 (1H, m, $CH_AH_B$), 1.79-1.71 (1H, m, $CH_AH_B$), 1.66-1.43 (11H, m, $CH_2$+3x$CH_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$), 155.9 (C), 147.6 (C), 146.1 (C), 134.6 (C), 130.5 (CH), 129.0 (CH), 119.8 (CH), 107.8 (CH), 107.5 (CH), 100.7 ($CH_2$), 79.6 (C), 53.3 (CH), 47.3 ($CH_2$), 28.4 (3x$CH_3$), 28.1 ($CH_2$), 24.6 ($CH_2$), 21.5 ($CH_2$); ***m/z*** (EI) 331 ($[M]^+$, 13 %), 275 (38), 194 (100), 150 (14), 140 (14), 136 (28), 135 (46); **HRMS** (EI) Found: $[M]^+$, 331.1775. $C_{19}H_{25}O_4N$ requires 331.1778.

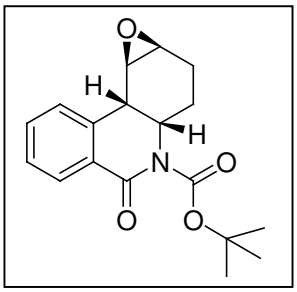
**(1a*SR*,3a*SR*,9b*SR*,9c*RS*)-1a,3,3a,5,9b,9c-Hexahydro-2*H*-1-oxa-4-aza-cyclopropa[*c*]phenanthrene-4-carboxylic acid *tert*-butyl ester 212**



To a solution of mCPBA (42 mg, 0.22 mmol) in $CH_2Cl_2$ (4 ml) at r.t. was added dropwise $\Delta^{1,2}$ phenanthridine **96b** (20 mg, 0.07 mmol) in $CH_2Cl_2$ (1 ml). The reaction was stirred for 2 h at r.t. then diluted with $CH_2Cl_2$ (15 ml) and washed with $Na_2CO_3$ (3 x 15 ml, sat. aq.). The organics were dried, concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 10:1) to afford epoxy phenanthridine **212** as a colourless oil (12 mg, 57%) and epoxy phenanthridone **213** as a colourless oil (8 mg, 36%).

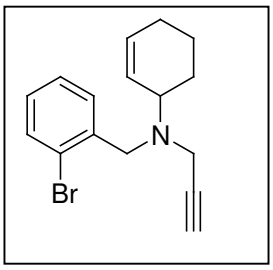
**$R_f$** [hexane:EtOAc, 3:1] = 0.54; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2976, 1693 (C=O), 1234 (C-O); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.42 (1H, d, *J* 6.9, Ar*H*), 7.30-7.25 (2H, m, 2xAr*H*), 7.19 (1H, d, *J* 7.2, Ar*H*), 4.77 (1H, d, *J* 16.4, C$H_X$$H_Y$Ar), 4.29 (1H, br s, NC*H*$CH_2$), 4.26 (1H, d, *J* 16.4, $CH_X$$H_Y$Ar), 3.60-3.57 (2H, m, C*H*OCH+C*H*$CH_2$), 3.23 (1H, t, *J* 3.7, CHOC*H*), 2.12-2.03 (1H, m, C$H_A$$H_B$), 1.97-1.89 (1H, m, $CH_A$$H_B$), 1.51-1.40 (11H, m, C$H_2$+3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 157.3 (C), 134.7 (C), 134.3 (C), 127.1 (CH), 126.7 (CH), 126.3 (CH), 126.1 (CH), 79.8 (C), 55.3 (CH), 51.8 (CH), 47.2 (CH), 43.9 ($CH_2$), 37.1 (CH), 28.4 (3x$CH_3$), 21.7 ($CH_2$), 21.6 ($CH_2$); ***m/z*** (EI) 301 ([M]$^+$, 1 %), 244 ([M-$^t$Bu]$^+$, 100), 228 (18), 172 (22); **HRMS** (EI) Found: [M]$^+$, 301.1672. $C_{18}H_{23}NO_3$ requires 301.1673. This compound was also fully characterised by NOESY 2D NMR studies.

**(1a*SR*,3a*SR*,9b*SR*,9c*RS*)-5-Oxo-1a,3,3a,5,9b,9c-hexahydro-2*H*-1-oxa-4-aza-cyclopropa[*c*]phenanthrene-4-carboxylic acid *tert*-butyl ester 213**



**$R_f$** [hexane:EtOAc, 3:1] = 0.38; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2979, 1715 (C=O), 1691 (C=O), 1244 (C-O); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 8.21 (1H, d, *J* 7.8, 1.4, Ar*H*), 7.58 (1H, td, *J* 7.5, 1.5, Ar*H*), 7.73 (1H, d, *J* 7.7, Ar*H*), 7.42 (1H, t, *J* 7.7, Ar*H*), 4.56 (1H, ddd, *J* 12.2, 5.1, 3.2, NC*H*$CH_2$), 3.97-3.96 (1H, m, C*H*$CH_2$), 3.91 (1H, t, *J* 5.8, C*H*OCH), 3.27 (1H, t, *J* 4.1, CHOC*H*), 2.16-2.07 (1H, m, $CH_AH_B$), 1.98-1.89 (1H, m, $CH_AH_B$), 1.63-1.39 (11H, m, $CH_2$+3x$CH_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 162.9 (C), 152.7 (C), 136.9 (C), 133.2 (CH), 129.8 (CH), 128.9 (C), 127.5 (CH), 124.7 (CH), 83.4 (C), 77.1 (CH), 55.2 (CH), 51.2 (CH), 35.5 (CH), 27.9 (3x$CH_3$), 22.2 ($CH_2$), 21.6 ($CH_2$); ***m/z*** (EI) 315 ($[M]^+$, 7 %), 260 (59), 216 (43), 146 (69), 57 (100); **HRMS** (EI) Found: $[M]^+$, 315.1467. $C_{18}H_{21}NO_4$ requires 315.1465.

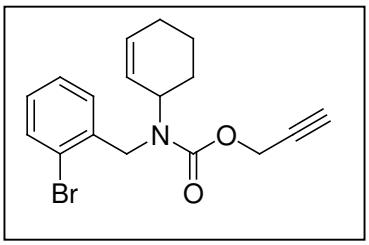
**(2-Bromo-benzyl)-cyclohex-3-enyl-prop-2-ynyl-amine 94f**




To a suspension of amine hydrochloride **93** (100 mg, 0.330 mmol) in DMF (5 ml) at r.t. was added $K_2CO_3$ (137 mg, 1.00 mmol) and the reaction stirred for 10 mins. Propargyl bromide (148 µl, 80 % by $^{w}/_{w}$. in toluene, 1.66 mmol) was added dropwise and the reaction stirred for 16 h. The reaction was diluted with $Et_2O$ (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.), and the combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. The resultant oil was purified using flash chromatography (hexane:EtOAc, 100:15) to afford propargyl amine **94f** as a colourless oil (103 mg, 99%).

**$R_f$** [hexane:EtOAc, 3: 1] = 0.89; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3299(C≡C-H), 2931, 1439, 1025; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.59 (1H, d, *J* 7.6, Ar*H*), 7.56 (1H, dd, *J* 7.9, 1.2, Ar*H*), 7.29 (1H, td, *J* 7.4, 1.2, Ar*H*), 7.10 (1H, td, *J* 7.8, 1.4, Ar*H*), 5.89-5.76 (2H, m, C*H*=C*H*), 3.91 (1H, d, *J* 15.0, C$H_X$$H_Y$Ar), 3.82 (1H, d, *J* 15.0, C$H_X$$H_Y$Ar), 3.56-3.53 (1H, m, C*H*N), 3.38 (2H, d, *J* 2.4, C$H_2$C≡CH), 2.23 (1H, t, *J* 2.4, ≡C*H*), 2.03-1.84 (4H, m, 2xC$H_2$), 1.69-1.44 (2H, m, C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 138.7 (C), 132.5 (CH), 130.6 (CH), 130.4 (CH), 129.7 (CH), 128.1 (C), 127.1 (CH), 124.2 (C), 81.4 (C), 72.2 (CH), 57.6 (CH), 52.9 ($CH_2$), 39.3 ($CH_2$), 25.2 ($CH_2$), 24.8 ($CH_2$), 21.2 ($CH_2$); ***m/z*** (EI) 305 ([$^{81Br}$M]$^+$, 19 %), 303 ([$^{79Br}$M]$^+$, 19), 277 (64), 275 (65), 251 (33), 249 (35), 213 (42), 171 (97), 169 (100), 106 (85); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 303.0618. $C_{16}H_{18}N^{79}Br$ requires 303.0617.

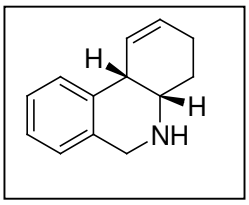
**(2-Bromo-benzyl)-cyclohex-3-enyl-carbamic acid prop-2-ynyl ester 94h**




To a suspension of amine hydrochloride **93** (100 mg, 0.33 mmol) in $CH_2Cl_2$ (10 ml) at 0 $^oC$ was added $Et_3N$ (182 µl, 1.32 mmol) and propargyl chloroformate (130 µl, 1.32 mmol). The reaction was allowed to warm to r.t. and stirred for 16 h. The reaction was diluted with $CH_2Cl_2$ (10 ml) and washed with HCl (3 x 10 ml, 1 M aq.). The combined organics were concentrated under reduced pressure to afford Poc-amine **94h** as a colourless oil (130 mg, 99%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.73; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3298 (C≡C-H), 2937, 1703 (C=O), 1442, 1409; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.52 (1H, d, *J* 7.7, Ar*H*), 7.30-7.24 (2H, m, 2xAr*H*), 7.10 (1H, td, *J* 7.3, 2.2, Ar*H*), 5.87-5.84 (1H, m, C*H*=CH), 5.48-5.43 (1H, m, CH=C*H*), 4.86 (1H, br s, C*H*N), 4.77-4.71 (2H, m, C$H_2$C≡CH), 4.50 (1H, d, *J* 17.3, C$H_X$H$_Y$Ar), 4.44 (1H, d, *J* 17.3, CH$_X$$H_Y$Ar), 2.45-2.37 (1H, m, ≡*CH*), 2.02-1.90 (3H, m, C$H_2$ +C$H_A$H$_B$), 1.80-1.70 (1H, m, CH$_A$$H_B$), 1.70-1.49 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.8 (C), 138.1 (C), 132.4 (CH), 131.9 (CH), 128.0 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 122.1 (C), 78.4 (C), 74.2 (CH), 54.0 (CH), 52.9 ($CH_2$), 47.6 ($CH_2$), 28.0 ($CH_2$), 24.4 ($CH_2$), 21.2 ($CH_2$); ***m/z*** (EI) 349 ([$^{81Br}$M]$^+$, 13 %), 347 ([$^{79Br}$M]$^+$, 14), 310 (99), 308 (100), 178 (57), 171 (88), 169 (93); **HRMS** (EI) Found: [$^{79Br}$M]$^+$, 347.0513. $C_{17}H_{18}O_2N^{79}Br$ requires 347.0515.

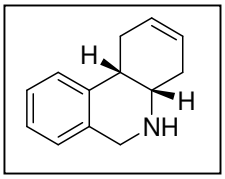
**(4a*SR*,10b*SR*)-3,4,4a,5,6,10b-Hexahydro-phenanthridine 245**




Flash vacuum pyrolysis of Boc-protected $\Delta^{1,2}$ isomer phenanthridine **96b** [500 mg, $T_f$ 600 $^oC$, $T_i$ 140 $^oC$, P 3.2 x $10^{-2}$ Torr, t 0.5 h], followed by Kugelrohr distillation (70 $^oC$, 0.7 Torr) gave amine **245** as a yellow oil (193 mg, 60%).

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.36; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3274 (NH), 3019, 2920, 1671 (C=C), 1449, 1260 (CN); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.22-7.21 (2H, m, 2xAr*H*), 7.17-7.14 (1H, m, Ar*H*), 7.03 (1H, d, *J* 7.5, Ar*H*), 5.74-5.71 (1H, m, C*H*=CH), 5.66-5.62 (1H, m, CH=C*H*), 4.12 (1H, d, *J* 16.3, C$H_X$$H_Y$Ar), 4.04 (1H, d, *J* 16.3, CH$_X$$H_Y$Ar), 3.36 (1H, br s, NC*H*CH), 3.32-3.28 (1H, m, NCHC*H*), 2.25-2.03 (2H, m, C$H_2$), 2.03-1.89 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 138.4 (C), 135.7 (C), 130.2 (CH), 129.1 (CH), 126.4 (CH), 125.8 (CH), 125.7 (2xCH), 50.4 (CH), 48.3 ($CH_2$), 38.0 (CH), 27.4 ($CH_2$), 20.0 ($CH_2$); ***m/z*** (EI) 185 ($[M]^+$, 77 %), 170 (21), 168 (18), 131 (38), 130 (72), 128 (46); **HRMS** (EI) Found: $[M]^+$, 185.1196. $C_{13}H_{15}N$ requires 185.1199.

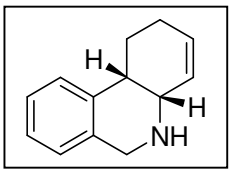
**(4a*SR*,10b*SR*)-1,4,4a,5,6,10b-Hexahydro-phenanthridine 246**




Flash vacuum pyrolysis of Boc-protected $\Delta^{2,3}$ isomer phenanthridine **97b** [900 mg, $T_f$ 600 $^oC$, $T_i$ 140 $^oC$, P 3.2 x $10^{-2}$ Torr, t 0.5 h], followed by Kugelrohr distillation (70 $^oC$, 0.7 Torr) gave amine **246** as a yellow oil (500 mg, 81%).

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.34; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3284 (NH), 3021, 2902, 1654 (C=C), 1453, 1260 (CN); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.17-7.13 (2H, m, 2xAr*H*), 7.09-7.02 (2H, m, Ar*H*), 5.73-5.66 (2H, m, C*H*=C*H*), 4.24 (1H, d, *J* 16.5, C$H_X$$H_Y$Ar), 4.15 (1H, d, *J* 16.5, CH$_X$$H_Y$Ar), 3.23 (1H, br d, *J* 4.0, NC*H*CH), 2.81 (1H, ddd, *J* 10.1, 6.4, 2.7, NCHC*H*), 2.65-2.59 (1H, m, C$H_A$$H_B$), 2.34-2.28 (1H, m, CH$_A$$H_B$), 2.15-2.10 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 141.0 (C), 134.2 (C), 128.2 (CH), 126.0 (CH), 125.9 (CH), 125.8 (CH), 124.7 (CH), 124.1 (CH), 49.9 (CH), 48.5 ($CH_2$), 35.3 (CH), 31.9 ($CH_2$), 30.1 ($CH_2$); ***m/z*** (EI) 185 ($[M]^+$, 10 %), 130 (100); **HRMS** (EI) Found: $[M]^+$, 185.1202. $C_{13}H_{15}N$ requires 185.1199.

**(4a*SR*,10b*SR*)-1,2,4a,5,6,10b-Hexahydro-phenanthridine 247**



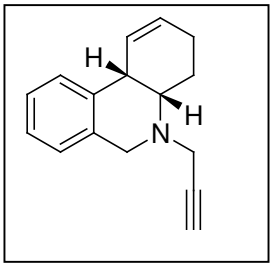

Flash vacuum pyrolysis of Boc-protected $\Delta^{3,4}$ isomer phenanthridine **98b** [320 mg, $T_f$ 600 °C, $T_i$ 140 °C, P 3.2 x $10^{-2}$ Torr, t 0.5 h], followed by Kugelrohr distillation (70 °C, 0.7 Torr) gave amine **247** as a yellow oil (190 mg, 71%).

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.37; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3283 (NH), 3020, 2902, 1654 (C=C), 1453, 1260 (CN); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.23-7.13 (3H, m, 3xAr*H*), 7.03 (1H, d, *J* 7.2, Ar*H*), 5.96-5.85 (2H, m, C*H*=C*H*), 4.05 (1H, d, *J* 16.6, C$H_X$$H_Y$Ar), 4.00 (1H, d, *J* 16.9, C$H_X$$H_Y$Ar), 3.46 (1H, br s, NC*H*CH), 2.74 (1H, dt, *J* 12.6, 3.6, NCHC*H*), 2.22-1.62 (4H, m, 2xC$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 139.3 (C), 135.8 (C), 130.0 (CH), 129.2 (CH), 128.3 (CH), 126.1 (CH), 125.7 (CH), 125.5 (CH), 50.7 (CH), 48.2 ($CH_2$), 36.5 (CH), 27.5 ($CH_2$), 25.8 ($CH_2$); ***m/z*** (EI) 185 ($[M]^+$, 10 %), 130 (100); **HRMS** (EI) Found: $[M]^+$, 185.1202. $C_{13}H_{15}N$ requires 185.1199.

**General procedure L - Propargylation**

To a solution of the appropriate phenanthridine (1 eq) in acetone (5 ml) was added $K_2CO_3$ (3 eq) followed by relevant alkylating agent (1.1 eq). The reaction was heated at 60 $^oC$ for the stated time and then concentrated under reduced pressure. The crude product was purified by flash chromatography to the desired alkyl amine.

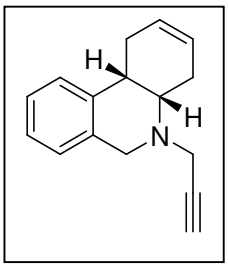
**(4a*SR*,10b*SR*)-5-(Prop-2'-ynyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 96f**




General procedure **L** was followed using amine **245** (150 mg, 0.81 mmol), acetone (5 ml), $K_2CO_3$ (368 mg, 2.67 mmol), and propargyl bromide (100 µl, 80 % $^w/_w$ in toluene, 0.89 mmol). After 2 h, flash chromatography ($CH_2Cl_2$) afforded propargyl amine **96f** as a yellow oil (103 mg, 57%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.83; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3290 (C≡C-H), 2925, 1696; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.27-7.10 (3H, m, 3xAr*H*), 7.10 (1H, d, *J* 7.2, Ar*H*), 5.79 (2H, s, C*H*=C*H*), 4.01 (1H, d, *J* 15.0, C$H_X$H$_Y$Ar), 3.83 (1H, dd, *J* 17.4, 2.4, C$H_P$H$_Q$C≡CH), 3.81 (1H, d, *J* 15.0, CH$_X$$H_Y$Ar), 3.56 (1H, dd, *J* 17.4, 2.4, CH$_P$$H_Q$C≡CH), 3.56 (1H, br s, NC*H*CH), 3.16 (1H, br s, NCHC*H*), 2.28 (1H, t, *J* 2.4, ≡C*H*), 2.14-2.00 (3H, m, C$H_2$+C$H_A$H$_B$), 1.87-1.75 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 137.3 (C), 133.8 (C), 129.8 (CH), 128.0 (CH), 126.5 (CH), 126.4 (CH), 126.1 (CH), 125.6 (CH), 78.3 (C), 73.4 (CH), 53.8 (CH), 53.4 ($CH_2$), 42.3 ($CH_2$), 39.2 (CH), 23.2 ($CH_2$), 21.9 ($CH_2$); ***m/z*** (EI) 223 ($[M]^+$, 59 %), 222 (100), 208 (16), 184 (17), 168 (36), 140 (34); **HRMS** (EI) Found: $[M]^+$, 223.1354. $C_{16}H_{17}N$ requires 223.1356.

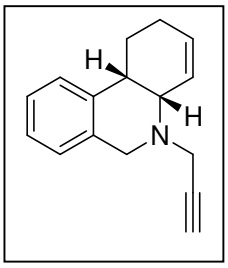
**(4a*SR*,10b*SR*)-5-(Prop-2'-ynyl)-1,4,4a,5,6,10b-hexahydro-phenanthridine 97f**



General procedure **L** was followed using amine **246** (50 mg, 0.27 mmol), acetone (2 ml), $K_2CO_3$ (112 mg, 0.81 mmol) and propargyl bromide (33 µl, 80 % $^{w}/_{w}$ in toluene, 0.30 mmol). After 2 h, flash chromatography ($CH_2Cl_2$) afforded propargyl amine **97f** as a colourless oil (45 mg, 75%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.89; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3292 (C≡C-H), 2925, 1663, 1604, 1430; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.17-7.14 (2H, m, 2xAr*H*), 7.12-7.08 (2H, m, 2xAr*H*), 5.76-5.72 (1H, m, C*H*=CH), 5.67-5.63 (1H, m, CH=C*H*), 4.10 (1H, d, *J* 15.2, C$H_X$H$_Y$Ar), 3.88 (1H, d, *J* 15.2, CH$_X$$H_Y$Ar), 3.75 (1H, dd, *J* 15.3, 2.3, CH$_P$$H_Q$C≡CH), 3.49 (1H, dd, *J* 15.3, 2.3, C$H_P$H$_Q$C≡CH), 3.08-3.05 (1H, m, NC*H*CH), 2.99 (1H, td, *J* 7.9, 2.4, NCHC*H*), 2.53-2.43 (1H, m, C$H_A$H$_B$), 2.38-2.13 (3H, m, C$H_2$+CH$_A$$H_B$), 2.26 (1H, t, *J* 2.3, ≡C*H*); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 140.2 (C), 134.0 (C), 127.0 (CH), 126.5 (CH), 126.3 (CH), 125.8 (CH), 125.7 (CH), 122.9 (CH), 78.3 (C), 73.4 (CH), 54.4 ($CH_2$), 53.3 (CH), 42.2 ($CH_2$), 37.6 (CH), 31.4 ($CH_2$), 26.4 ($CH_2$); ***m/z*** (EI) 223 ($[M]^+$, 6 %), 222 (6), 168 (100), 129 (25); **HRMS** (EI) Found: $[M]^+$, 223.1350. $C_{16}H_{17}N$ requires 223.1356.

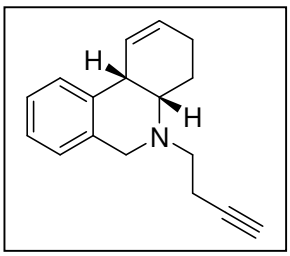
**(4a*SR*,10b*SR*)-5-(Prop-2'-ynyl)-1,2,4a,5,6,10b-hexahydro-phenanthridine 98f**




General procedure **L** was followed using amine **247** (52 mg, 0.18 mmol), acetone (5 ml), $K_2CO_3$ (76 mg, 0.55 mmol) and propargyl bromide (18 µl, 80% $^{w}/_{w}$ in toluene, 0.20 mmol). After 2 h, flash chromatography ($CH_2Cl_2$) afforded propargyl amine **98f** as a yellow oil (37 mg, 91%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.84; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3291 (C≡C-H), 3027, 2925, 1663; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.20-7.04 (3H, m, 3xAr*H*), 7.05 (1H, d, *J* 7.3, 2xAr*H*), 6.02-5.93 (2H, m, C*H*=C*H*), 3.98 (1H, d, *J* 15.1, C$H_X$H$_Y$Ar), 3.82 (1H, dd, *J* 17.2, 2.3, C$H_P$H$_Q$C≡CH), 3.78 (1H, d, *J* 15.1, CH$_X$$H_Y$Ar), 3.51 (1H, dd, *J* 17.2, 2.4, CH$_P$$H_Q$C≡CH), 3.26 (1H, br s, NC*H*CH), 2.84 (1H, dt, *J* 11.2, 3.5, NCHC*H*), 2.27 (1H, t, *J* 2.3, ≡C*H*), 2.16-2.04 (3H, m, C$H_2$+C$H_A$H$_B$), 1.85-1.76 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 138.8 (C), 134.5 (C), 132.1 (CH), 128.2 (CH), 126.2 (CH), 126.0 (CH), 125.6 (CH), 125.5 (CH), 78.5 (C), 73.1 (CH), 54.0 ($CH_2$), 54.0 (CH), 42.3 ($CH_2$), 38.0 (CH), 27.7 ($CH_2$), 25.7 ($CH_2$); ***m/z*** (EI) 223 ([M]$^+$, 30 %), 222 (47), 194 (10), 169 (100), 129 (15).

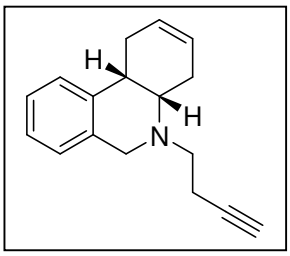
**(4a*SR*,10b*SR*)-5-But-3-ynyl-3,4,4a,5,6,10b-hexahydro-phenanthridine 96g**




General procedure **L** was followed using amine **245** (150 mg, 0.81 mmol), acetone (5 ml), $K_2CO_3$ (368 mg, 2.67 mmol) and 4-bromo-1-butyne (84 µl, 0.89 mmol). After 16 h flash chromatography ($CH_2Cl_2$) afforded homopropargyl amine **96g** as a yellow oil (105 mg, 55%).

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.9; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3295 (C≡C-H), 3023, 2929; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.29 (1H, d, *J* 7.6, Ar*H*), 7.19 (1H, t, *J* 7.5, Ar*H*), 7.13 (1H, t, *J* 7.4, Ar*H*), 7.03 (1H, d, *J* 7.5, Ar*H*), 6.10-6.04 (1H, m, C*H*=CH), 5.82-5.77 (1H, m, CH=C*H*), 3.87 (1H, d, *J* 15.3, C$H_X$H$_Y$Ar), 3.74 (1H, d, *J* 15.3, CH$_X$$H_Y$Ar), 3.60 (1H, br s, NC*H*CH), 3.18-3.11 (1H, m, NCHC*H*), 2.97-2.92 (2H, m, C$H_2$), 2.52-2.47 (2H, m, C$H_2$), 2.17-2.10 (2H, m, C$H_2$), 2.01 (1H, t, *J* 2.6, ≡C*H*), 1.83-1.75 (1H, m, C$H_A$H$_B$), 1.71-1.61 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 137.4 (C), 133.1 (C), 128.7 (CH), 127.6 (CH), 127.4 (CH), 126.5 (CH), 126.3 (CH), 125.3 (CH), 82.8 (C), 69.0 (CH), 56.2 (CH), 52.9 ($CH_2$), 51.0 ($CH_2$), 37.8 (CH), 24.2 ($CH_2$), 20.0 ($CH_2$), 17.3 ($CH_2$); ***m/z*** (EI) 237 ([M]$^+$, 5 %), 198 (100), 141 (18), 128 (16); **HRMS** (EI) Found: [M]$^+$, 237.1511. $C_{17}H_{19}N$ requires 237.1512.

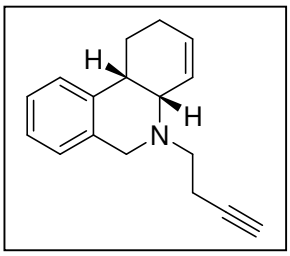
**(4a*SR*,10b*SR*)-5-But-3-ynyl-1,4,4a,5,6,10b-hexahydro-phenanthridine 97g**




General procedure **L** was followed using amine **246** (40 mg, 0.216 mmol), acetone (1.5 ml), $K_2CO_3$ (90 mg, 0.65 mmol) and 4-bromo-1-butyne (22 µl, 0.24 mmol). After 16 h flash chromatography ($CH_2Cl_2$–$CH_2Cl_2$:MeOH, 95:5) afforded homopropargyl amine **97g** as a yellow oil (32 mg, 63%).

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.65; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3294 (C≡C-H), 2925, 1649 (C=C), 1452; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.18-7.14 (3H, m, 3xAr*H*), 7.07-7.05 (1H, m, Ar*H*), 5.69-5.66 (1H, m, C*H*=CH), 5.60-5.56 (1H, m, CH=C*H*), 3.92 (2H, s, C$H_2$Ar), 3.16-3.12 (2H, m, 2xC*H*), 2.97-2.92 (2H, m, C$H_2$), 2.62-2.53 (1H, m, C$H_A$H$_B$), 2.49-2.42 (3H, m, C$H_2$+CH$_A$$H_B$), 2.21-2.19 (2H, m, C$H_2$), 2.00 (1H, t, *J* 2.7, ≡CH); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 138.4 (C), 134.2 (C), 126.2 (2xCH), 126.0 (CH), 125.6 (CH), 125.5 (CH), 124.1 (CH), 82.8 (C), 69.0 (CH), 54.8 (CH), 52.9 ($CH_2$), 52.8 ($CH_2$), 36.8 (CH), 29.3 ($CH_2$), 24.0 ($CH_2$), 16.8 ($CH_2$); ***m/z*** (EI) 237 ($[M]^+$, 6 %), 198 (56), 182 (100), 144 (65), 128 (21); **HRMS** (EI) Found: $[M]^+$, 237.1509. $C_{17}H_{19}N$ requires 237.1512.

**(4a*SR*,10b*SR*)-5-But-3-ynyl-1,2,4a,5,6,10b-hexahydro-phenanthridine 98g**



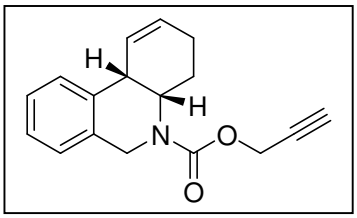

General procedure **L** was followed using amine **247** (70 mg, 0.38 mmol), acetone (4 ml), $K_2CO_3$ (156 mg, 1.13 mmol) and 4-bromo-1-butyne (38 µl, 0.42 mmol). After 16 h flash chromatography ($CH_2Cl_2$) afforded homopropargyl amine **98g** as a yellow oil (65 mg, 73 %).

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.9; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3294 (C≡C-H), 3022, 2925, 1648 (C=C); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.28 (1H, d, *J* 7.4, Ar*H*), 7.19 (1H, t, *J* 7.3, Ar*H*), 7.12 (1H, t, *J* 7.3, Ar*H*), 7.01 (1H, d, *J* 7.4, Ar*H*), 5.88 (1H, d, *J* 10.7, C*H*=CH), 5.82 (1H, d, *J* 11.9, CH=C*H*), 3.91 (1H, d, *J* 15.3, C$H_X$$H_Y$Ar), 3.69 (1H, d, *J* 15.3, CH$_X$$H_Y$Ar), 3.48 (1H, br s, NC*H*CH), 3.08-3.02 (1H, m, NCHC*H*), 3.00-2.89 (2H, m, C$H_2$), 2.46 (2H, t, *J* 7.1, C$H_2$), 2.24-2.18 (1H, m, C$H_A$H$_B$), 2.01-1.93 (3H, m, C$H_2$+≡CH), 1.90-1.85 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 137.3 (C), 134.6 (C), 131.7 (CH), 127.3 (CH), 126.3 (CH), 126.2 (CH), 125.7 (CH), 125.4 (CH), 82.8 (C), 68.9 (CH), 56.3 (CH), 52.0 (2x$CH_2$), 35.9 (CH), 26.5 ($CH_2$), 23.4 ($CH_2$), 17.6 ($CH_2$); ***m/z*** (EI) 237 ([M]$^+$, 8 %), 199 (100), 169 (62), 167 (65), 164 (35), 141 (70); **HRMS** (EI) Found: [M]$^+$, 237.1515. $C_{17}H_{19}N$ requires 237.1512.

**Tetrahydro-phenanthridine-5-carboxylic acid prop-2-ynyl ester 96h-98h**

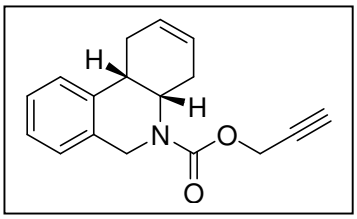
To a solution of amines **245-247** (271 mg, 1.46 mmol) at 0 $^{o}$C in $CH_2Cl_2$ (15 ml) was added $Et_3N$ (822 µl, 5.85 mmol) and propargyl chloroformate (573 µl, 5.85 mmol) dropwise. The reaction was allowed to warm to r.t. and stirred for 16 h. The reaction was diluted with $CH_2Cl_2$ (15 ml) and washed with HCl (3 x 15 ml, 1 M aq.). The combined organics were concentrated under reduced pressure to afford Poc-amide isomer mixture **96h-98h** as a colourless oil (290 mg, 74 %). Flash chromatography (hexane:EtOAc, 100:5) afforded **96h** (54 mg, 14%), **97h** (48 mg, 12%), **98h** (38 mg, 10%) and mixture **96h-98h** (130 mg, 33%) all colourless oils.

**(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-3*H*-phenanthridine-5-carboxylic acid prop-2-ynyl ester 96h**



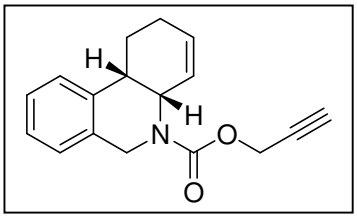

**$R_f$** [hexane:EtOAc, 3:1] = 0.64; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3291 (C≡C-H), 1700 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.30 (1H, d, *J* 7.6, Ar*H*), 7.24 (1H, td, *J* 7.2, 1.8, Ar*H*), 7.18 (1H, tdd, *J* 7.2, 1.4, 0.7, ArH), 7.12 (1H, d, *J* 7.6, Ar*H*), 6.16-6.11 (1H, m, C*H*=CH), 5.88-5.84 (1H, m, CH=C*H*), 4.81 (1H, d, *J* 16.5, C$H_X$H$_Y$Ar), 4.76 (2H, s, C$H_2$C≡CH), 4.48 (1H, br s, NCHC*H*), 4.46 (1H, d, *J* 16.5, CH$_X$$H_Y$Ar), 3.60 (1H, br s, NC*H*), 2.46 (1H, t, *J* 1.2, ≡*CH*), 2.34-2.22 (1H, m, C$H_A$H$_B$), 2.17-2.07 (1H, m, CH$_A$$H_B$), 1.76-1.74 (1H, m, C$H_C$H$_D$), 1.67-1.55 (1H, m, CH$_C$$H_D$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.6 (C), 137.4 (C), 131.7 (C), 128.3 (CH), 127.6 (CH), 127.0 (2xCH), 126.0 (2xCH), 78.5 (C), 74.3 (CH), 52.8 ($CH_2$), 50.7 (CH), 43.6 ($CH_2$), 37.1 (CH), 25.0 ($CH_2$), 24.0 ($CH_2$); ***m/z*** (EI) 267 ([M]$^+$, 34 %), 228 (100), 213 (50), 187 (37), 167 (59), 141 (21), 128 (30); **HRMS** (EI) Found: [M]$^+$, 267.1252. $C_{17}H_{17}O_2N$ requires 237.1512.

**(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-1*H*-phenanthridine-5-carboxylic acid prop-2-ynyl ester 97h**



**$R_f$** [hexane:EtOAc, 3:1] = 0.60; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3289 (C≡C-H), 1703 (C=O), 1695; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.27-7.13 (4H, m, Ar*H*), 5.71-5.68 (1H, m, C*H*=CH), 5.45-5.40 (1H, m, CH=C*H*), 4.84-4.80 (2H, m, C$H_2$), 4.66 (1H, d, *J* 16.2, C$H_P$H$_Q$C≡CH), 4.59 (1H, d, *J* 16.2, CH$_P$$H_Q$C≡CH), 4.51 (1H, br s, NC*H*), 3.23 (1H, t, *J* 4.8, NCHC*H*), 2.88 (1H, dd, *J* 18.3, 5.2, C$H_A$H$_B$), 2.67-2.59 (1H, m, CH$_A$$H_B$), 2.47 (1H, t, *J* 2.4, ≡*CH*), 2.32-2.22 (1H, m, C$H_C$H$_D$), 1.56-1.45 (1H, m, CH$_C$$H_D$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.5 (C), 136.2 (C), 133.5 (C), 127.0 (CH), 126.4 (CH), 126.3 (CH), 125.2 (CH), 125.0 (CH), 123.8 (CH), 78.7 (C), 74.3 (CH), 52.8 ($CH_2$), 50.5 (CH), 45.0 ($CH_2$), 35.6 (CH), 27.1 ($CH_2$), 26.3 ($CH_2$); ***m/z*** (EI) 267 ($[M]^+$, 17 %), 228 (100), 184 (38), 167 (72); **HRMS** (EI) Found: $[M]^+$, 267.1252. $C_{17}H_{17}O_2N$ requires 267.1254.

**(4a*SR*,10b*SR*)-2,4a,6,10b-Tetrahydro-1*H*-phenanthridine-5-carboxylic acid prop-2-ynyl ester 98h**

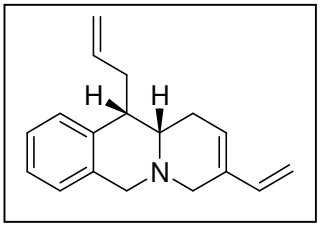


**$R_f$** [hexane:EtOAc, 3:1] = 0.64; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3292 (C≡*C-H*), 1703 (C=O), 1433; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.36 (1H, d, *J* 7.6, Ar*H*), 7.28-7.15 (2H, m, 2xAr*H*), 7.07 (1H, d, *J* 7.3, ArH), 5.75-5.72 (1H, m, C*H*=CH), 5.54 (1H, d, *J* 10.1, CH=C*H*), 5.17 (1H, br s, NCHC*H*), 4.92 (1H, d, *J* 16.6, C$H_X$H$_Y$Ar), 4.78-4.77 (2H, m, C$H_2$C≡CH), 4.33 (1H, d, *J* 16.6, NCHC*H*), 3.35 (1H, br s, NC*H*), 2.47-2.40 (2H, m, ≡C*H*+C$H_A$H$_B$), 2.04-1.99 (1H, m, CH$_A$$H_B$), 1.95-1.72 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.6 (C), 135.0 (C), 133.4 (C), 131.4 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 125.9 (CH), 125.8 (CH), 78.5 (C), 74.3 (CH), 53.0 ($CH_2$), 50.8 (CH), 42.8 ($CH_2$), 34.2 (CH), 25.1 ($CH_2$), 20.3 ($CH_2$); ***m/z*** (EI) 267 ($[M]^+$, 14 %), 228 (100), 184 (33), 167 (40); **HRMS** (EI) Found: $[M]^+$, 267.1254. $C_{17}H_{17}O_2N$ requires 267.1254.

**General procedure M - RRM reactions of amines**

To a solution of the appropriate amine (1 eq) in $CH_2Cl_2$ (1 ml) was added HCl (1-2 ml, 1 M in $Et_2O$) and the solvent removed under reduced pressure. The resultant hydrochloride salt was dissolved in $CH_2Cl_2$ (10 ml) and degassed with ethylene for 10 mins. Hoveyda-Grubbs catalyst 2$^{nd}$ generation (0.15 eq) was added and the reaction stirred under an atmosphere of ethylene for 40 h at r.t. The crude product was washed with NaOH (3 x 20 ml, 1 M aq.) and the combined organics dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography to afford the appropriate product.

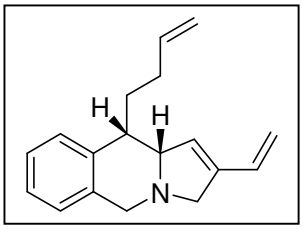
**(11*SR*,11a*SR*)-11-Allyl-3-vinyl-1,6,11,11a-tetrahydro-4*H*-pyrido[1,2-*b*]isoquinoline 237**




General procedure **M** was followed using propargyl amine **97f** (50 mg, 0.22 mmol), $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$), then $CH_2Cl_2$ (10 ml) and Hoveyda-Grubbs catalyst 2$^{nd}$ generation (21 mg, 33.6 μmol). Flash chromatography ($CH_2Cl_2$:MeOH, 100-100:1) afforded isoquinoline **237** as a colourless oil (40 mg, 71%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.31; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 2925, 1655, 1636; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.33 (1H, d, *J* 6.6, Ar*H*), 7.18-7.14 (2H, m, 2xAr*H*), 7.04-7.02 (1H, m, Ar*H*), 6.34 (1H, dd, *J* 17.8, 10.9, CC*H*=$CH_2$), 6.00-5.88 (1H, dddd, *J* 17.1, 10.3, 8.4, 5.6, $CH_2$C*H*=$CH_2$), 5.86-5.82 (1H, m, $CH_2$C*H*=C), 5.16 (1H, dq, *J* 17.1, 1.2, $CH_2$CH=C*H*$_C$H$_D$), 5.12 (1H, br d, *J* 10.3, $CH_2$CH=CH$_C$*H*$_D$), 5.06 (1H, d, *J* 17.8, CCH=C*H*$_E$H$_F$), 4.97 (1H, d, *J* 10.9, CCH=CH$_E$*H*$_F$), 4.07 (1H, d, *J* 15.8, C*H*$_X$H$_Y$Ar), 3.78 (1H, d, *J* 15.8, CH$_X$*H*$_Y$Ar), 3.77 (1H, d, *J* 17.0, NC*H*$_P$H$_Q$), 3.46 (1H, d, *J* 17.0, NCH$_P$*H*$_Q$), 3.34-3.30 (2H, m, NC*HCH*), 2.91-2.84 (1H, m, $CH_2$=CHC*H*$_A$H$_B$), 2.19-2.10 (1H, m, $CH_2$=CHCH$_A$*H*$_B$), 2.06-1.94 (2H, m, CHC*H*$_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 137.6 (CH), 136.8 (CH), 135.6 (C), 134.4 (C), 131.8 (C), 126.9 (CH), 126.3 (CH), 126.2 (CH), 126.0 (CH), 125.7 (CH), 116.4 ($CH_2$), 110.6 ($CH_2$), 53.8 (CH), 52.3 ($CH_2$), 50.0 ($CH_2$), 40.6 (CH), 34.2 ($CH_2$), 20.1 ($CH_2$); ***m/z*** (ESI+) 252 ([M+H]$^+$, 98 %), 211 (15), 172 (100), 145 (8), 131 (100); **HRMS** (EI) Found: [M]$^+$, 251.1675. $C_{18}H_{21}N$ requires 251.1669. This compound was also fully characterised by 2D COSY, NOESY and HSQC NMR experiments.

**(10*SR*,10a*SR*)-10-(But-3'-enyl)-2-vinyl-3,5,10,10a-tetrahydro-pyrrolo[1,2-*b*]isoquinoline 238**

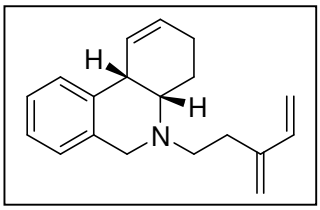



General procedure **M** was followed using propargyl amine **98f** (10 mg, 45 µmol), $CH_2Cl_2$ (1 ml) and HCl (1 ml, 1 M in $Et_2O$), then $CH_2Cl_2$ (5 ml) and Hoveyda-Grubbs catalyst 2$^{nd}$ generation (4.2 mg, 6.7 µmol). Flash chromatography ($CH_2Cl_2$:MeOH, 100-100:5) afforded isoquinoline **238** as a yellow oil (9 mg, 80%). This compound was not stable therefore full characterisation was not possible.

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.36; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.18-7.16 (3H, m, 3xAr*H*), 7.15-7.10 (1H, m, Ar*H*), 6.52 (1H, dd, *J* 17.5, 10.9, CC*H*=$CH_2$), 5.89-5.77 (2H, m, CHC*H*=C+$CH_2$C*H*=$CH_2$), 5.14 (1H, br d, *J* 10.9, CCH=C$H_C$$H_T$), 5.08 (1H, br d, *J* 17.5, CCH=C$H_C$$H_T$), 5.03 (1H, dq, *J* 17.1, 1.5, $CH_2$CH=C$H_C$$H_T$), 4.94 (1H, dq, *J* 11.2, 1.9, $CH_2$CH=C$H_C$$H_T$), 4.08 (1H, d, *J* 14.6, C$H_X$$H_Y$Ar), 3.93-3.84 (4H, m, C$H_X$$H_Y$Ar+NC$H_2$+C*H*), 2.96-2.92 (1H, m, C*H*), 2.24-2.15 (2H, m, C$H_2$), 1.86-1.78 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 131.0 (CH), 128.9 (CH), 128.1 (2xCH), 126.6 (CH), 126.0 (CH), 125.6 (CH), 114.8 ($CH_2$), 114.2 ($CH_2$), 58.2 (CH), 55.5 ($CH_2$), 53.6 ($CH_2$), 41.3 (CH), 32.0 ($CH_2$), 30.7 ($CH_2$). $^{13}$C data was assigned using HSQC data, therefore four quaternary carbons remain unassigned.

This compound was also characterised by 2D COSY NMR.

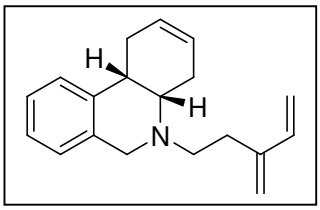
**(4a*SR*,10b*SR*)-5-(3'-Methylene-pent-4'-enyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 96j**




General procedure **M** was followed using homopropargyl amine **96g** (41 mg, 0.17 mmol), $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) then $CH_2Cl_2$ (10 ml) and Hoveyda-Grubbs catalyst 2$^{nd}$ generation (16 mg, 26 μmol). Flash chromatography ($CH_2Cl_2$–$CH_2Cl_2$:MeOH, 100:0.5) afforded phenanthridine **96j** as a colourless oil (31 mg, 69%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.48; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3854, 3745, 2925, 1653, 1457; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.30 (1H, d, *J* 7.3, Ar*H*), 7.20 (1H, td, *J* 7.0, 1.5, Ar*H*), 7.13 (1H, td, *J* 6.3, 1.8, Ar*H*), 7.05 (1H, d, *J* 7.3, Ar*H*), 6.41 (1H, dd, *J* 17.6, 10.3, CC*H*=$CH_2$), 6.12-6.05 (1H, m, CHC*H*=CH), 5.85-5.77 (1H, m, CH=C*H*$CH_2$), 5.32 (1H, d, *J* 17.6, CH=C$H_U$$H_V$), 5.13-5.08 (3H, m, CH=$CH_U$$H_V$+C$H_2$), 3.91 (1H, d, *J* 15.5, C$H_X$$H_Y$Ar), 3.77 (1H, d, *J* 15.3, $CH_X$$H_Y$Ar), 3.62 (1H, br s, NC*H*CH), 3.16 (1H, ddd, *J* 10.0, 5.3, 2.8, NCHC*H*), 2.94-2.75 (2H, m, C$H_2$$CH_2$), 2.59-2.52 (2H, m, $CH_2$C$H_2$), 2.17-2.08 (2H, m, =CHC$H_2$), 1.86-1.76 (1H, m, CHNC$H_A$$H_B$), 1.71-1.58 (1H, m, CHNC$H_A$$H_B$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 144.6 (C), 138.7 (CH), 137.5 (C), 133.3 (C), 128.8 (CH), 127.6 (CH), 127.4 (CH), 126.4 (CH), 126.3 (CH), 125.3 (CH), 116.5 ($CH_2$), 113.3 ($CH_2$), 56.5 (CH), 53.4 ($CH_2$), 51.2 ($CH_2$), 37.8 (CH), 29.6 ($CH_2$), 29.4 ($CH_2$), 24.3 ($CH_2$); ***m/z*** (EI) 265 ([M]$^+$, 6 %), 198 (100); **HRMS** (EI) Found: [M]$^+$, 265.1827. $C_{19}H_{23}N$ requires 265.1825. This compound was also characterised by 2D COSY NMR.

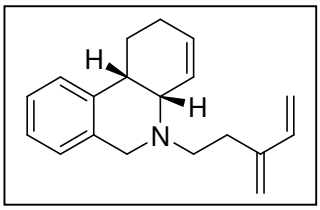
**(4a*SR*,10b*SR*)-5-(3'-Methylene-pent-4'-enyl)-1,4,4a,5,6,10b-hexahydro-phenanthridine 97j**



General procedure **M** was followed using homopropargyl amine **97g** (41 mg, 0.17 mmol), $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$), then $CH_2Cl_2$ (10 ml) Hoveyda-Grubbs catalyst 2$^{nd}$ generation (16 mg, 26 μmol). Flash chromatography ($CH_2Cl_2$–$CH_2Cl_2$:MeOH, 100:0.5) afforded phenanthridine **97j** as a colourless oil (25 mg, 54%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.51; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 2907, 1646 (C=C); **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.19-7.13 (3H, m, 3xAr*H*), 7.09-7.07 (1H, m, Ar*H*), 6.40 (1H, dd, *J* 17.5, 10.7, CC*H*=$CH_2$), 5.69-5.66 (1H, m, C*H*=CH), 5.58-5.55 (1H, m, CH=C*H*), 5.32 (1H, d, *J* 17.5, CH=C$H_U$H$_V$), 5.31 (1H, br s, C=C$H_R$H$_S$), 5.11-5.07 (2H, m, CH=CH$_U$$H_V$+C=CH$_R$$H_S$), 5.12 (2H, s, C$H_2$), 3.94 (2H, s, C$H_2$Ar), 3.20-3.10 (2H, m, NC*H*C*H*), 2.92-2.81 (2H, m, C$H_2$), 2.60-2.43 (4H, m, 2xC$H_2$), 2.22-2.18 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 144.7 (C), 138.8 (CH), 138.4 (C), 134.6 (C), 126.3 (CH), 126.1 (CH), 126.0 (CH), 125.6 (CH), 125.4 (CH), 124.5 (CH), 116.5 ($CH_2$), 113.3 ($CH_2$), 55.0 (CH), 53.3 ($CH_2$), 53.0 ($CH_2$), 36.8 (CH), 29.2 ($CH_2$), 28.8 ($CH_2$), 23.6 ($CH_2$); ***m/z*** (EI) 265 ([M]$^+$, 7 %), 198 (16), 197 (100), 169 (12); **HRMS** (EI) Found: [M]$^+$, 265.1827. $C_{19}H_{23}N$ requires 265.1825.

**(4a*SR*,10b*SR*)-5-(3'-Methylene-pent-4'-enyl)-1,2,4a,5,6,10b-hexahydro-phenanthridine 97j**



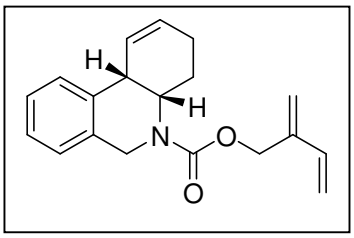

General procedure **M** was followed using homopropargyl amine **98g** (12 mg, 50.6 μmol), $CH_2Cl_2$ (1 ml) and HCl (1 ml, 1 M in $Et_2O$), then $CH_2Cl_2$ (10 ml) and Hoveyda-Grubbs catalyst 2$^{nd}$ generation (5 mg, 7.6 μmol). Flash chromatography ($CH_2Cl_2$–$CH_2Cl_2$:MeOH, 100:0.5) afforded phenanthridine **98j** as a colourless oil (9 mg, 67%).

**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.42; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3022, 2925, 1453; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.29 (1H, d, *J* 9.9, Ar*H*), 7.21 (1H, t, *J* 7.5, Ar*H*), 7.14 (1H, t, *J* 7.5, Ar*H*), 7.03 (1H, d, *J* 7.5, Ar*H*), 6.38 (1H, dd, *J* 17.6, 10.6, CC*H*=$CH_2$), 5.89 (2H, br s, C*H*=C*H*), 5.32 (1H, d, *J* 17.6, CH=C$H_U$$H_W$), 5.12-5.07 (3H, m, C$H_2$+CH=C$H_U$$H_W$), 4.01 (1H, d, *J* 15.2, C$H_X$$H_Y$Ar), 3.76 (1H, d, *J* 15.5, C$H_X$$H_Y$Ar), 3.63 (1H, br s, NC*H*CH), 3.14 (1H, br s, NCHC*H*), 2.99-2.94 (1H, m, C$H_A$$H_B$), 2.91-2.83 (1H, m, C$H_A$$H_B$), 2.62-2.50 (2H, m, C$H_2$), 2.36-2.26 (1H, m, C$H_C$$H_D$), 1.99-1.90 (3H, m, C$H_C$$H_D$+C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 144.6 (C), 138.8 (CH), 137.2 (C), 134.9 (C), 131.4 (CH), 127.2 (CH), 126.3 (CH), 126.2 (CH), 125.7 (CH), 125.4 (CH), 116.4 ($CH_2$), 113.3 ($CH_2$), 56.5 (CH), 52.4 ($CH_2$), 52.0 ($CH_2$), 35.8 (CH), 29.5 ($CH_2$), 26.5 ($CH_2$), 23.2 ($CH_2$); ***m/z*** (EI) 265 ([M]$^+$, 8 %), 212 (70), 198 (100), 145 (30), 143 (46); **HRMS** (EI) Found: [M]$^+$, 265.1826. $C_{19}H_{23}N$ requires 265.1825.

**General procedure N - RRM reactions of Poc analogues**

A solution of the appropriate amide (1 eq) in $CH_2Cl_2$ (10 ml) was degassed with ethylene for 10 mins. Hoveyda-Grubbs catalyst 2nd generation (0.15 eq) was added and the reaction stirred under an atmosphere of ethylene for 40 h at r.t. The crude product was concentrated under reduced pressure and purified by flash chromatography to afford the appropriate product.

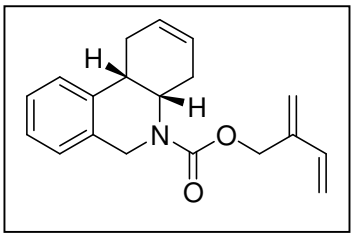
**(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-3*H*-phenanthridine-5-carboxylic acid 2-methylene-but-3-enyl ester 96k**



General procedure **N** was followed using *Poc* amide **96h** (25 mg, 93.5 µmol), $CH_2Cl_2$ (5 ml) and Hoveyda-Grubbs catalyst 2nd generation (9 mg, 14.0 µmol). Flash chromatography (hexane:EtOAc, 20:1) afforded phenanthridine **96k** as a colourless oil (20 mg, 73%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.79; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 2929, 1695 (C=O), 1418; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.30 (1H, d, *J* 7.4, Ar*H*), 7.23 (1H, td, *J* 7.6, 1.4, Ar*H*), 7.18 (1H, td, *J* 7.9, 1.1, Ar*H*), 7.12 (1H, d, *J* 6.8, Ar*H*), 6.41 (1H, dd, *J* 18.1, 11.1, CC*H*=$CH_2$), 6.11-6.11 (1H, m, CHC*H*=CH), 5.88-5.85 (1H, m, CH=C*H*$CH_2$), 5.33 (1H, d, *J* 18.1, CCH=C$H_UH_V$), 5.29 (1H, br s, C=C$H_RH_S$), 5.23 (1H, br s, C=C$H_RH_S$), 5.15 (1H, d, *J* 11.1, CCH=C$H_UH_V$), 4.87 (2H, s, OC$H_2$), 4.80 (1H, d, *J* 16.4, C$H_XH_Y$Ar), 4.48 (1H, br s, NC*H*), 4.46 (1H, d, *J* 16.4, C$H_XH_Y$Ar), 3.60 (1H, br s, NCHC*H*), 2.31-2.22 (1H, m, CHC$H_AH_B$), 2.15-2.08 (1H, m, CHC$H_AH_B$), 1.78-1.73 (1H, m, NCHC$H_CH_D$), 1.66-1.64 (1H, m, NCHC$H_CH_D$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 155.2 (C), 141.7 (C), 137.4 (C), 136.1 (2xCH), 131.9 (C), 128.3 (2xCH), 127.6 (CH), 126.9 (2xCH), 125.9 (CH), 117.3 ($CH_2$), 114.5 ($CH_2$), 64.5 ($CH_2$), 50.5 (CH), 43.6 ($CH_2$), 36.8 (CH), 25.1 ($CH_2$); ***m/z*** (EI) 295 ($[M]^+$, 48 %), 268 (50), 228 (100), 184 (43), 167 (40); **HRMS** (EI) Found: $[M]^+$, 295.1567. $C_{19}H_{21}NO_2$ requires 295.1567. This compound was also characterised by 2D COSY NMR.

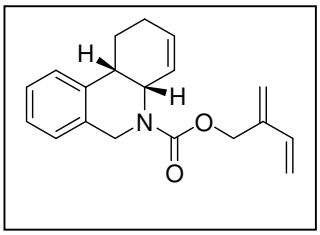
**(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-1*H*-phenanthridine-5-carboxylic acid 2-methylene-but-3-enyl ester 97k**



General procedure **N** was followed using *Poc* amide **96h** (24 mg, 89.9 µmol),$CH_2Cl_2$ (4 ml) and Hoveyda-Grubbs catalyst 2$^{nd}$ generation (8.5 mg, 13.5 µmol). Flash chromatography (hexane:EtOAc, 20:1) afforded phenanthridine **97k** as a colourless oil (16 mg, 60%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.66; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3026, 2929, 1699 (C=O), 1412; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.27-7.17 (4H, m, 4xAr*H*), 6.42 (1H, dd, *J* 18.1, 11.1, CC*H*=$CH_2$), 5.71-5.67 (1H, m, C*H*=CH), 5.44-5.40 (1H, m, CH=C*H*), 5.34 (1H, d, *J* 18.1, CCH=C$H_U$$H_W$), 5.30 (1H, br s, C=C$H_R$$H_S$), 5.25 (1H, br s, C=C$H_R$$H_S$), 5.16 (1H, d, *J* 11.1, CCH=C$H_U$$H_W$), 4.92 (1H, d, *J* 13.3, OC$H_P$$H_Q$), 4.85 (1H, d, *J* 13.3, OC$H_P$$H_Q$), 4.66 (1H, d, *J* 16.1, C$H_X$$H_Y$Ar), 4.60 (1H, d, *J* 16.1, C$H_X$$H_Y$Ar), 4.35 (1H, br s, NC*H*), 3.23 (1H, br s, NCHC*H*), 2.88 (1H, dd, *J* 18.2, 5.3, CHC$H_A$$H_B$), 2.64-2.55 (1H, m, CHC$H_A$$H_B$), 2.28-2.23 (1H, m, CHNC$H_C$$H_D$), 1.61-1.49 (1H, m, CHNC$H_C$$H_D$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 155.1 (C), 141.3 (C), 136.1 (C+CH), 133.4 (C), 126.8 (CH), 126.4 (CH), 126.2 (CH), 125.0 (CH), 124.9 (CH), 123.7 (CH), 117.3 ($CH_2$), 114.5 ($CH_2$), 64.4 ($CH_2$), 53.3 (CH), 50.2 ($CH_2$), 44.8 ($CH_2$), 35.5 (CH), 26.1 ($CH_2$); ***m/z*** (EI) 295 ([M]$^+$, 12 %), 241 (100), 228 (13), 198 (13), 196 (25), 174 (12), 167 (10), 130 (69); **HRMS** (EI) Found: [M]$^+$, 295.1567. $C_{19}H_{21}NO_2$ requires 295.1567. This compound was also characterised by 2D COSY NMR.

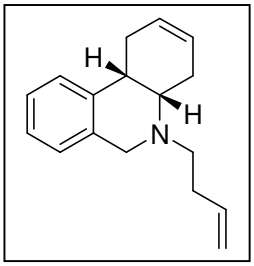
**(4a*SR*,10b*SR*)-2,4a,6,10b-Tetrahydro-1*H*-phenanthridine-5-carboxylic acid 2-methylene-but-3-enyl ester 98k**



General procedure **N** was followed using *Poc* amide **98h** (19 mg, 71.0 µmol), $CH_2Cl_2$ (4 ml) and Hoveyda-Grubbs catalyst 2$^{nd}$ generation (7 mg, 10.7 µmol). Flash chromatography ($CH_2Cl_2$) to afford phenanthridine **98k** as a colourless oil (20 mg, 96%).

**$R_f$** [hexane:EtOAc, 3:1] = 0.63; **$\upsilon_{max}$** ($CHCl_3$)/cm$^{-1}$ 3025, 2927, 1700 (C=O), 1430; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.36 (1H, d, *J* 7.5, Ar*H*), 7.27-7.17 (2H, m, 2xAr*H*), 7.06 (1H, d, *J* 7.3, Ar*H*), 6.39 (1H, dd, *J* 17.8, 10.8, CC*H*=$CH_2$), 5.76-5.68 (1H, m, CH=C*H*$CH_2$), 5.54 (1H, br d, *J* 10.8, NCHC*H*=CH), 5.31 (1H, d, *J* 17.8, CCH=C$H_U$$H_V$), 5.26 (1H, s, C=C$H_R$$H_S$), 5.22 (1H, s, C=C$H_R$$H_S$), 5.14 (1H, d, *J* 10.5, CCH=C$H_U$$H_V$), 5.13 (1H, br s, NC*H*CH), 4.93 (1H, d, *J* 16.8, C$H_X$$H_Y$Ar), 4.86 (2H, s, OC$H_2$), 4.32 (1H, d, *J* 16.8, C$H_X$$H_Y$Ar), 3.33 (1H, br s, NCHC*H*), 2.44-2.39 (1H, m, CHC$H_A$$H_B$), 2.04-1.99 (1H, m, CHC$H_A$$H_B$), 1.88-1.81 (2H, m, =CHC$H_2$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.3 (C), 141.8 (C), 136.2 (CH), 135.1 (C), 133.7 (C), 131.3 (CH), 127.3 (CH), 126.7 (CH), 126.6 (CH), 125.8 (2xCH), 117.1 ($CH_2$), 114.5 ($CH_2$), 64.7 ($CH_2$), 50.7 (CH), 42.8 ($CH_2$), 34.2 (CH), 25.2 ($CH_2$), 20.3 ($CH_2$); ***m/z*** (EI) 295 ([M]$^+$, 28 %), 228 (93), 199 (90), 184 (27), 167 (41); **HRMS** (EI) Found: [M]$^+$, 295.1567. $C_{19}H_{21}NO_2$ requires 295.1567. This compound was also characterised by 2D COSY NMR.

**(4a*SR*,10b*SR*)-5-(But-3'-enyl)-1,4,4a,5,6,10b-hexahydro-phenanthridine 97m**



General procedure **L** was followed using amine **246** (70 mg, 0.38 mmol), acetone (4 ml), $K_2CO_3$ (157 mg, 1.13 mmol) and 4-bromo-1-butene (46 µl, 0.45 mmol). After 16 h, flash chromatography ($CH_2Cl_2$) afforded butenyl amine **97m** (84 mg, 93%) as a yellow oil.

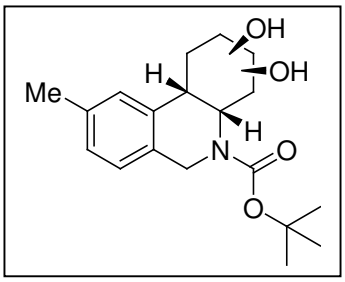
**$R_f$** [hexane:EtOAc, 3:1] = 0.68; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3024, 2924, 1647, 1446; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.22-7.11 (3H, m, 3xAr*H*), 7.08-7.05 (1H, m, Ar*H*), 5.87 (1H, ddt, *J* 17.1, 10.2, 6.8, C*H*=$CH_2$), 5.71-5.64 (1H, m, C*H*=CH), 5.61-5.54 (1H, m, CH=C*H*), 5.10 (1H, dq, *J* 17.1, 1.7, CH=C$H_T$$H_C$), 5.02 (1H, dq, *J* 10.2, 1.0, CH=C$H_T$$H_C$), 3.90 (2H, s, C$H_2$Ar), 3.18-3.11 (2H, m, NC*H*C*H*), 2.87-2.56 (3H, m, C$H_2$+C$H_A$$H_B$), 2.46-2.29 (3H, m, C$H_2$+C$H_A$$H_B$), 2.17 (2H, br s, C$H_2$); **$^{13}$C NMR** δ (69.2 MHz, $CDCl_3$) 138.4 (C), 136.7 (CH), 134.7 (C), 126.3 (CH), 126.1 (CH), 125.9 (CH), 125.5 (CH), 125.4 (CH), 124.4 (CH), 115.4 ($CH_2$), 54.8 (CH), 53.6 ($CH_2$), 52.9 ($CH_2$), 36.8 (CH), 31.3 ($CH_2$), 29.2 ($CH_2$), 23.5 ($CH_2$); ***m/z*** (EI) 239 ($[M]^+$, 2 %), 212 (10), 198 (100), 185 (36), 144 (37); **HRMS** (EI) Found: $[M]^+$, 239.1671. $C_{17}H_{21}N$ requires 239.1669.

## 6.4 Experimental for Chapter four

### General procedure P - Dihydroxylation

To a solution of the appropriate phenanthridines (1 eq) in THF and $H_2O$ at r.t was added $OsO_4$ (0.07 eq, 2.5% $^w/_w$ in $^t$BuOH) and NMO (3 eq) and the reaction was stirred for 16 h. The reaction mixture was poured onto $Na_2SO_3$ (30 ml, sat. aq.) and extracted with EtOAc (3 x 30 ml). The combined organics were dried ($MgSO_4$), concentrated under reduced pressure and purified to afford the appropriate mixture of diols. Purification by flash chromatography afforded either a mixture of the isolated isomers/diol mixture, or purely the diol mixture. In cases where the isolated isomers were not obtained, further purification by HPLC afforded the corresponding isolated diols.

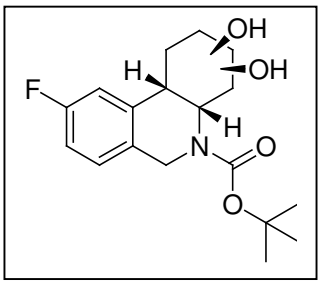
**Dihydroxy-9-methyl-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206a-208a ($\Delta^{1,2}$, $\Delta^{2,3}$, $\Delta^{3,4}$ isomer)**




General procedure **P** was followed using phenanthridines **195a**-**197a** (84 mg, 0.282 mmol), THF (165 µl), $H_2O$ (820 µl), $OsO_4$ (247 µl, 2.5% $^{w}/_{w}$ in $^{t}$BuOH, 19.7 µmol) and NMO (132 mg, 0.846 mmol). Flash chromatography ($CH_2Cl_2$-$CH_2Cl_2$:MeOH, 100:2) afforded mixture of diols **206a**-**208a** (73 mg, 78%). Further isolation of the individual diol products **206a**-**208a** was not found to be possible by HPLC so these compounds were taken on as a mixture.

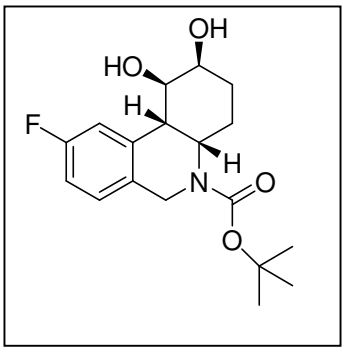
**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.57; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3421 (OH), 1664 (C=O); ***m/z*** (EI) 319 ($[M]^+$, 2 %), 262 ($[M-^{t}Bu]^+$, 100), 218 ($[M-Boc]^+$, 22), 184 (75).

**9-Fluoro-3,4-dihydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206b-208b**



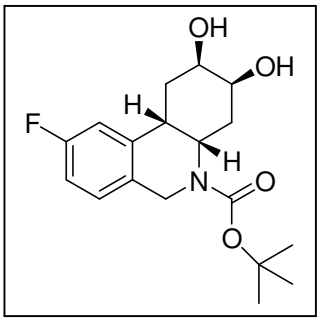

General procedure **P** was followed using phenanthridines **195b**-**197b** (50 mg, 0.165 mmol), THF (920 µl), $H_2O$ (184 µl), $OsO_4$ (144 µl, 2.5% $^{w}/_{w}$ in $^{t}$BuOH, 11.5 µmol) and NMO (58 mg, 0.495 mmol). Flash chromatography ($CH_2Cl_2$:MeOH, 100:2) afforded mixture of diols **206b**-**208b** (46 mg, 82%). HPLC (EtOAc:hexane, 3:1) of this mixture afforded $\Delta^{1,2}$ diol **206b** (10 mg, 18%), $\Delta^{2,3}$ diol **207b** (15.3 mg, 2 %), $\Delta^{3,4}$ diol **208b** (11.4 mg, 20%), and mixed diol fractions (9 mg, 16%) giving an overall yield (45.7 mg, 82%), all colourless oils.

**(1*RS*,2*SR*,4a*SR*,10b*SR*)-9-Fluoro-1,2-dihydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206b ($\Delta^{1,2}$ isomer)**



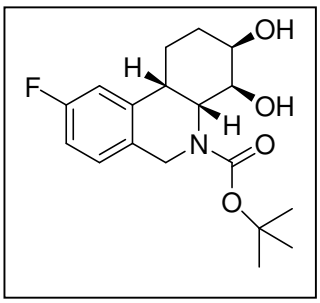

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.43; **$R_t$** (EtOAc:hexane, 3:1, flow rate: 10 ml/min) = 15 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$3425 (OH), 2976, 2931, 1664 (C=O), 1367, 1167; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.13-7.04 (2H, m, 2xAr*H*), 6.92 (1H, td, *J* 10.9, 2.6, Ar*H*), 4.70-4.62 (3H, m, 2xC*H*+C$H_X$H$_Y$Ar), 4.31 (1H, d, *J* 16.9, CH$_X$*H*$_Y$*Ar*), 3.73-3.68 (1H, m, C*H*), 3.37 (1H, br s, C*H*), 2.51 (1H, br s, O*H*), 1.92-1.84 (1H, m, C$H_A$H$_B$), 1.70-1.52 (2H, m, CH$_A$*H*$_B$+C$H_C$H$_D$), 1.51 (9H, s, 3xC$H_3$), 1.91-1.82 (1H, m, CH$_C$*H*$_D$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 161.9 (1C, d, *J* 245.2, C), 154.8 (C), 135.3 (1C, d, *J* 6.9, C), 129.1 (C), 128.1 (1C, d, *J* 8.2, CH), 113.5 (1C, d, *J* 21.7, CH), 112.5 (1C, d, *J* 22.4, CH), 80.1 (C), 71.1 (CH), 67.4 (CH), 46.9 (CH), 43.0 ($CH_2$), 42.9 (CH), 28.4 (3x$CH_3$), 27.3 ($CH_2$), 24.2 ($CH_2$) ; ***m/z*** (EI) 337 ([M]$^+$, 1 %), 280 ([M-$^t$Bu]$^+$, 100), 236 ([M-Boc]$^+$, 61), 192 (19), 162 (26).

**(2*RS*,3*SR*,4a*SR*,10b*SR*)-9-Fluoro-2,3-dihydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 207b ($\Delta^{2,3}$ isomer)**



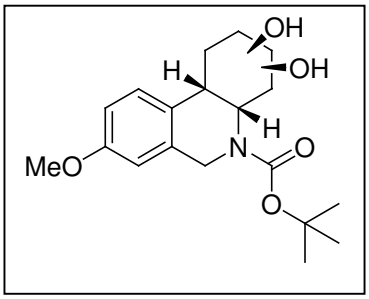

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.53; **$R_t$** (EtOAc:hexane, 3:1, flow rate: 10 ml/min) = 20 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3421 (OH), 2935, 1670 (C=O), 1412, 1167; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.17 (1H, d, *J* 10.1, Ar*H*), 7.11-7.07 (1H, m, Ar*H*), 6.91 (1H, td, *J* 8.3, 1.8, Ar*H*), 4.80-4.72 (1H, m, C*H*), 4.66 (1H, d, *J* 17.1, C$H_X$H$_Y$Ar), 4.31 (1H, d, *J* 17.0, CH$_X$*H*$_Y$*Ar*), 3.93 (1H, br s, C*H*), 3.64-3.60 (1H, m, C*H*), 3.23 (1H, br s, CH), 2.40-2.23 (2H, m, C$H_2$), 1.92-1.89 (1H, m, C$H_A$H$_B$), 1.52 (9H, s, 3xC$H_3$), 1.45-1.42 (1H, m, CH$_A$*H*$_B$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 164.9 (1C, d, *J* 133.4, C), 154.7 (C), 136.8 (C), 128.6 (C), 127.9 (1C, d, *J* 8.3, CH), 113.4 (1C, d, *J* 21.6, CH), 112.5 (1C, d, *J* 21.9, CH), 80.2 (C), 69.1 (CH), 66.6 (CH), 46.3 (CH), 42.8 ($CH_2$), 36.4 (CH), 31.3 ($CH_2$), 29.1 ($CH_2$), 28.4 (3x$CH_3$); ***m/z*** (EI) 337 ([M]$^+$, 1 %), 280 ([M-$^t$Bu])$^+$, 100), 236 ([M-Boc]$^+$, 27), 218 (19), 192 (35), 162 (34), 148 (24).

**(3*RS*,4*SR*,4a*RS*,10b*SR*)-9-Fluoro-3,4-dihydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 208b ($\Delta^{3,4}$ isomer)**



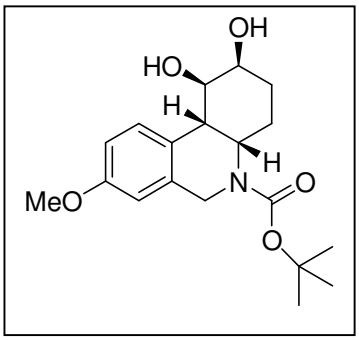

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.47; **$R_t$** (EtOAc:hexane, 3:1, flow rate: 8 ml/min) = 17 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3404 (OH), 2937, 1670 (C=O), 1421, 1169; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.11 (1H, dd, *J* 8.5, 5.7, Ar*H*), 7.03 (1H, dd, *J* 10.0, 1.7, Ar*H*), 6.92 (1H, m, Ar*H*), 4.73-4.61 (2H, m, C*H*+C$H_X$$H_Y$Ar), 4.41 (1H, d, *J* 16.4, C$H_X$$H_Y$*Ar*), 3.96 (1H, d, *J* 2.7, C*H*), 3.30-3.25 (2H, m, 2xC*H*), 2.85-2.72 (1H, m, C$H_A$$H_B$), 2.17-2.12 (1H, m, C$H_A$$H_B$), 1.87-1.82 (1H, m, C$H_C$$H_D$), 1.60-1.50 (10H, m, CH$_C$$H_D$+3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 162.1 (1C, d, *J* 245.1, C), 155.2 (C), 137.1 (1C, d, *J* 2.8, C), 128.9 (C), 128.0 (1C, d, *J* 8.2, CH), 113.4 (1C, d, *J* 21.7, CH), 112.3 (1C, d, *J* 22.1, CH), 81.0 (C), 69.5 (2xCH), 52.7 (CH), 42.1 ($CH_2$), 37.1 (CH), 28.4 (3x$CH_3$), 25.4 ($CH_2$), 20.1 ($CH_2$); ***m/z*** (EI) 337 ($[M]^+$, 1 %), 281 (36), 280 ($[M-^tBu]^+$, 9), 236 ($[M-Boc]^+$, 100), 218 (11), 206 (12), 192 (13), 162 (40).

**Dihydroxy-8-methoxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206c-208c**



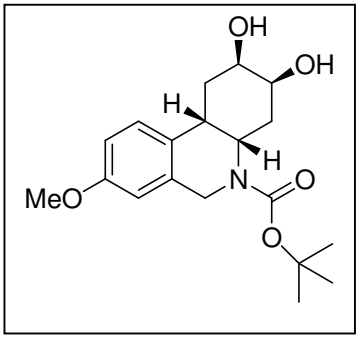

General procedure **P** was followed using phenanthridines **195c-197c** (152 mg, 0.482 mmol), THF (2.70 ml), $H_2O$ (541 µl), $OsO_4$ (423 µl, 2.5% $^w/_w$ in $^t$BuOH, 33.8 µmol) and NMO (226 mg, 1.93 mmol). Flash chromatography ($CH_2Cl_2$:MeOH, 100:1-10:1) afforded mixture of diols **195c-197c** (159 mg, 95%). HPLC (EtOAc:hexane, 4:1) of this mixture afforded $\Delta^{1,2}$ diol **206c** (21 mg, 13%), $\Delta^{2,3}$ diol **207c** (20 mg, 12%), $\Delta^{3,4}$ diol **208c** (32 mg, 19%), and mixed diol fractions (32 mg, 19%), giving a total yield (105 mg, 63%), all colourless oils.

**(1*RS*,2*SR*,4a*SR*,10b*SR*)-1,2-Dihydroxy-8-methoxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206c ($\Delta^{1,2}$ isomer)**



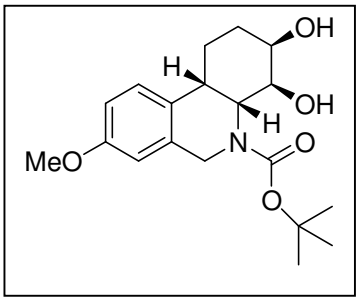

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.49; **$R_t$** (EtOAc:hexane, 4:1, flow rate: 10 ml/min) = 21 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3423 (OH), 2933, 1687 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.24 (1H, d, *J* 8.6, Ar*H*), 6.79 (1H, dd, *J* 8.6, 2.7, Ar*H*), 6.68 (1H, d, *J* 2.7, Ar*H*), 4.72-4.63 (3H, m, 2xC*H*+C$H_X$$H_Y$Ar), 4.30 (1H, d, *J* 17.1, C$H_X$$H_Y$Ar), 3.80 (3H, s, $CH_3$), 3.75-3.69 (1H, m, C*H*), 3.35 (1H, br s, C*H*), 2.60 (1H, br s, O*H*), 1.93-1.87 (1H, m, C$H_A$$H_B$), 1.69-1.64 (1H, m, C$H_A$$H_B$), 1.57-1.41 (11H, m, C$H_2$+3xC$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 157.9 (C), 154.8 (C), 134.6 (C), 126.5 (CH), 124.8 (C), 112.9 (CH), 111.5 (CH), 79.9 (C), 71.1 (CH), 67.3 (CH), 55.2 ($CH_3$), 46.8 (CH), 43.5 ($CH_2$), 42.0 (CH), 28.4 (3x$CH_3$), 27.3 ($CH_2$), 23.9 ($CH_2$); ***m/z*** (EI) 349 ($[M]^+$, 4 %), 292 ($[M-^tBu]^+$, 27), 248 ($[M-Boc]^+$, 21), 174 (22).

**(2*RS*,3*SR*,4a*SR*,10b*SR*)-2,3-Dihydroxy-8-methoxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 207c ($\Delta^{2,3}$ isomer)**



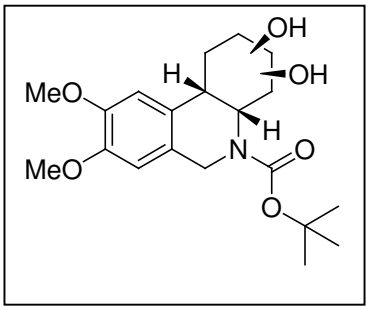

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.49; **$R_t$** (EtOAc:hexane, 4:1, flow rate: 10 ml/min) = 24 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3392 (OH), 2935, 1672 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.37 (1H, d, *J* 8.5, Ar*H*), 6.82 (1H, dd, *J* 8.5, 2.7, Ar*H*), 6.67 (1H, d, *J* 2.6, Ar*H*), 4.76-4.67 (2H, m, C*H*+C$H_X$$H_Y$Ar), 4.31 (1H, d, *J* 17.4, C$H_X$$H_Y$Ar), 3.92 (1H, d, *J* 3.1, C*H*), 3.81 (3H, s, C$H_3$), 3.66-3.61 (1H, m, C*H*), 3.21 (1H, m, C*H*), 2.45-2.42 (1H, m, C$H_A$$H_B$), 2.26-2.17 (1H, m, C$H_A$$H_B$), 1.91-1.86 (1H, m, C$H_C$$H_D$), 1.52 (9H, s, 3xC$H_3$), 1.41 (1H, t, *J* 7.3, C$H_C$$H_D$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 158.2 (C), 154.7 (C), 134.5 (C), 126.8 (CH), 126.5 (C), 113.0 (CH), 111.5 (CH), 79.9 (C), 69.6 (CH), 66.7 (CH), 55.2 ($CH_3$), 46.5 (CH), 43.7 ($CH_2$), 35.7 (CH), 31.3 ($CH_2$), 29.5 ($CH_2$), 28.5 (3x$CH_3$); ***m/z*** (EI) 349 ($[M]^+$, 5 %), 292 ($[M-^tBu]^+$, 38), 248 ($[M-Boc]^+$, 37), 204 (35), 174 (40), 160 (33).

**(3*RS*,4*SR*,4a*RS*,10b*SR*)-3,4-Dihydroxy-8-methoxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 208c ($\Delta^{3,4}$ isomer)**



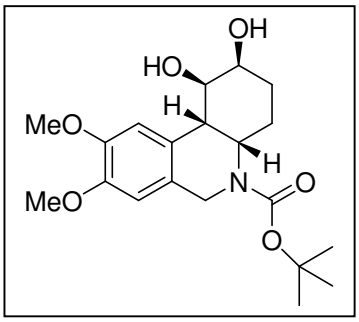

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.49; **$R_t$** (EtOAc:hexane, 4:1, flow rate: 10 ml/min) = 17 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3492 (OH), 2935, 1668 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.23 (1H, d, *J* 8.7, Ar*H*), 6.82 (1H, dd, *J* 5.9, 2.7, Ar*H*), 6.69 (1H, d, *J* 2.7, Ar*H*), 4.80-4.62 (2H, m, C*H*+C$H_X$H$_Y$Ar), 4.41 (1H, d, *J* 16.7, CH$_X$*H*$_Y$*Ar*), 3.94 (1H, d, *J* 2.8, C*H*), 3.81 (3H, s, C$H_3$), 3.34-3.31 (1H, m, C*H*), 3.24-3.22 (1H, m, C*H*), 2.23-2.21 (1H, m, C$H_A$H$_B$), 1.85-1.80 (1H, m, CH$_A$*H*$_B$), 1.57-1.52 (10H, s, C$H_C$H$_D$+3xC$H_3$), 1.43-1.39 (1H, m, CH$_C$*H*$_D$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 158.2 (2xC), 134.5 (C), 126.4 (CH), 123.4 (CH), 113.0 (CH), 111.6 (CH), 80.8 (C), 69.6 (2xCH), 55.3 ($CH_3$), 53.3 (CH), 46.8 ($CH_2$), 36.2 (CH), 28.4 (3x$CH_3$), 25.3 ($CH_2$), 20.1 ($CH_2$); ***m/z*** (EI) 349 ($[M]^+$, 21 %), 292 ($[M-^tBu)]^+$, 100), 257 (56), 248 ($[M-Boc]^+$, 33), 230 (61), 204 (55).

**Dihydroxy-8,9-dimethoxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206d-208d**



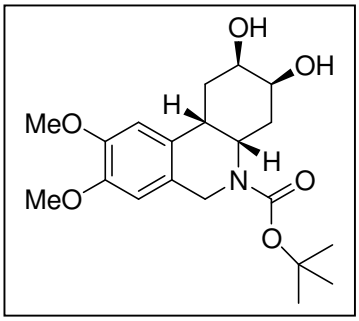

General procedure **P** was followed using phenanthridines **195d-197d** (30 mg, 87 µmol), THF (488 µl), $H_2O$ (98 µl), $OsO_4$ (76 µl, 2.5% $^w/_w$ in $^t$BuOH, 6.1 µmol) and NMO (31 mg, 0.26 mmol). Flash chromatography ($CH_2Cl_2$:MeOH, 100:5) afforded mixture of diols **206d-208d** (23 mg, 70 %). HPLC (EtOAc:hexane, 84:16) afforded $\Delta^{1,2}$ diol **206d** (2 mg, 6%), diol mixture **206d** and **207d** (6.2 mg, 19%) and $\Delta^{3,4}$ diol **208d** (10 mg, 30%), giving an overall yield (18.2 mg, 55%), all colourless oils.

**(1*RS*,2*SR*,4a*SR*,10b*SR*)-1,2-Dihydroxy-8,9-dimethoxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206d ($\Delta^{1,2}$ isomer)**




**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.48; **$R_t$** (EtOAc:hexane, 84:16, flow rate: 10 ml/min) = 38 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$3423 (OH), 2937, 1670 (C=O), 1520, 1406; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 6.83 (1H, s, Ar*H*), 6.61 (1H, s, Ar*H*), 4.70-4.64 (3H, m, 2xC*H*+C$H_X$H$_Y$Ar), 4.24 (1H, d, *J* 16.8, CH$_X$*H*$_Y$Ar), 3.87 (6H, s, 2xC$H_3$), 3.70-3.67 (1H, m, C*H*), 3.34 (1H, br s, C*H*), 1.93-1.89 (1H, m, C$H_A$H$_B$), 1.67-1.61 (2H, m, CH$_A$*H*$_B$+C$H_C$H$_D$), 1.53-1.45 (10H, m, CH$_C$*H*$_D$+3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 154.8 (C), 147.9 (C), 147.6 (C), 125.3 (C), 124.5 (C), 109.3 (CH), 108.6 (CH), 80.0 (C), 71.3 (CH), 67.5 (CH), 56.1 ($CH_3$), 55.8 ($CH_3$), 46.7 (CH), 42.9 ($CH_2$), 42.2 (CH), 28.4 (3x$CH_3$), 27.2 ($CH_2$), 23.8 ($CH_2$); ***m/z*** (EI) 379 ([M]$^+$, 2 %), 322 (100), 278 (6), 234 (4).

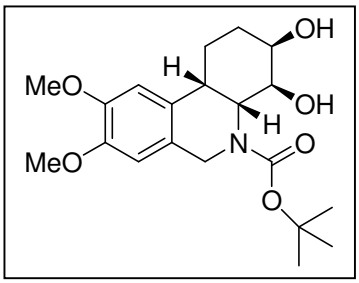
**(2*RS*,3*SR*,4a*SR*,10b*SR*)-2,3-Dihydroxy-8,9-dimethoxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 207d ($\Delta^{2,3}$ isomer)**




NMR Data for $\Delta^{2,3}$ isomer **207d** was deduced from $^1$H and $^{13}$C NMR of **206d** and **207d** mixture.

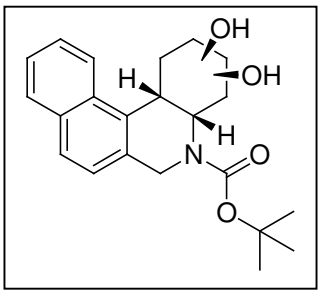
**$R_f$** [9: 1 $CH_2Cl_2$:MeOH] = 0.48; **$R_t$** (EtOAc:hexane, 84:16, flow rate: 10 ml/min) = 38 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3425 (OH), 2935, 1664 (C=O), 1520, 1259; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 6.94 (1H, s, Ar*H*), 6.60 (1H, s, Ar*H*), 4.75-4.63 (2H, m, C*H*+C$H_X$H$_Y$Ar), 4.25 (1H, d, *J* 16.8, CH$_X$*H*$_Y$Ar), 3.94 (1H, br s, C*H*), 3.89 (3H, s, C$H_3$), 3.87 (3H, s, C$H_3$), 3.63-3.60 (1H, m, C*H*), 3.20 (1H, br s, C*H*), 2.43-2.40 (1H, m, C$H_A$H$_B$), 2.28-2.19 (1H, m, CH$_A$*H*$_B$), 1.89-1.85 (1H, m, C$H_C$H$_D$), 1.66-1.61 (1H, m, CH$_C$*H*$_D$), 1.50 (9H, m, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 154.7 (C), 148.1 (C), 147.6 (C), 128.5 (C), 126.1 (C), 109.2 (CH), 108.6 (CH), 79.9 (C), 69.3 (CH), 66.8 (CH), 56.1 ($CH_3$), 55.8 ($CH_3$), 45.8 (CH), 42.9 ($CH_2$), 35.7 (CH), 31.1 ($CH_2$), 29.6 ($CH_2$), 28.4 (3x$CH_3$); ***m/z*** (EI) 379 ([M]$^+$, 2 %), 322 ([M-$^t$Bu]$^+$, 100), 278 (38), 190 (10).

**(3*RS*,4*SR*,4a*RS*,10b*SR*)-3,4-Dihydroxy-8,9-dimethoxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 208d ($\Delta^{3,4}$ isomer)**



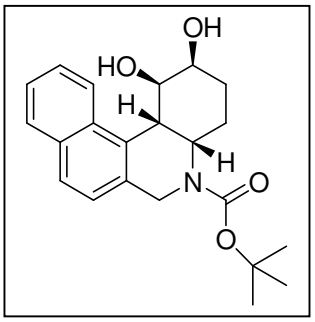

**$R_f$** [9: 1 $CH_2Cl_2$:MeOH] = 0.51; **$R_t$** (EtOAc:hexane, 84:16, flow rate: 10 ml/min) = 23 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3404 (OH), 2931, 1668 (C=O), 1518, 1419; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 6.80 (1H, s, Ar*H*), 6.63 (1H, s, Ar*H*), 4.66-4.60 (2H, m, C*H*+C$H_X$H$_Y$Ar), 4.37 (1H, d, *J* 16.8, CH$_X$*H*$_Y$Ar), 3.96 (1H, br s, C*H*), 3.88 (3H, s, OC$H_3$), 3.87 (3H, s, OC$H_3$), 3.35-3.31 (1H, m, C*H*), 3.22 (1H, br s, C*H*), 2.26-2.13 (2H, m, C$H_2$), 1.86-1.78 (1H, m, C$H_A$H$_B$), 1.53-1.42 (10H, m, CH$_A$*H*$_B$+3xC$H_3$); **$^{13}$C NMR** δ (62.9 MHz, $CDCl_3$) 157.7 (C), 148.0 (C), 147.6 (C), 127.6 (C), 125.2 (C), 109.4 (CH), 108.5 (CH), 80.8 (C), 71.2 (CH), 69.4 (CH), 56.0 ($CH_3$), 55.9 ($CH_3$), 52.7 (CH), 43.9 ($CH_2$), 36.3 (CH), 28.4 (3x$CH_3$), 25.4 ($CH_2$), 20.2 ($CH_2$); ***m/z*** (EI) 379 ([M]$^+$, 1 %), 322 ([M-$^t$Bu]$^+$, 2), 278 ([M-Boc]$^+$, 10).

**Dihydroxy-2,3,4,4a,6,12c-hexahydro-1*H*-benzo[*k*]phenanthridine-5-carboxylic acid *tert*-butyl ester 206e-208e**



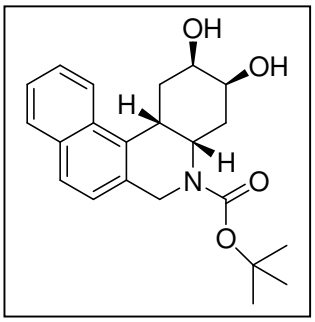

General procedure **P** was followed using phenanthridines **195e-197e** (130 mg, 0.39 mmol), THF (2.17 ml), $H_2O$ (434 µl), $OsO_4$ (338 µl, 2.5% $^w/_w$ in $^t$BuOH, 27.1 µmol) and NMO (136 mg, 1.16 mmol). Flash chromatography ($CH_2Cl_2$:MeOH, 100:0.5) afforded $\Delta^{1,2}$ diol **206e** (20 mg, 14%), $\Delta^{2,3}$ diol **207e** (40 mg, 28%), $\Delta^{3,4}$ diol **208e** (23 mg, 16%), and mixed diol (42 mg, 29%) giving a total yield (125 mg, 87%).

**(1*RS*,2*SR*,4a*SR*,12c*SR*)-1,2-Dihydroxy-2,3,4,4a,6,12c-hexahydro-1*H*-benzo[*k*]phenanthridine-5-carboxylic acid *tert*-butyl ester 206e ($\Delta^{1,2}$ isomer)**



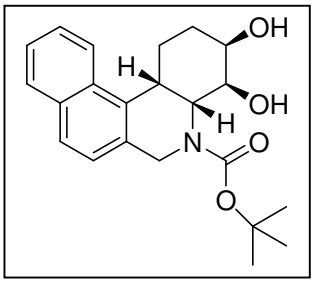

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.65; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3418 (OH), 2932, 1668 (C=O), 1393, 1163; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 8.08 (1H, d, *J* 8.5, Ar*H*), 7.85 (1H, d, *J* 7.9, Ar*H*), 7.70 (1H, d, *J* 8.3, Ar*H*), 7.54 (1H, t, *J* 7.9, Ar*H*), 7.47 (1H, t, *J* 7.9, Ar*H*), 7.26 (1H, d, *J* 8.3, Ar*H*), 5.11 (1H, d, *J* 15.9, C$H_X$H$_Y$Ar), 4.41 (1H, m, C*H*), 4.30 (1H, d, *J* 15.9, CH$_X$$H_Y$Ar), 4.17-4.28 (2H, m, 2xC*H*), 3.98-3.95 (1H, m, C*H*), 2.79 (1H, br s, O*H*), 2.27 (1H, br s, O*H*), 2.01-1.93 (2H, m, C$H_2$), 1.75-1.69 (2H, m, C$H_2$), 1.49 (9H, m, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 156.0 (C), 134.8 (C), 133.3 (C), 132.6 (C), 130.6 (C), 128.8 (CH), 126.6 (CH), 126.2 (CH), 125.4 (CH), 124.6 (CH), 122.6 (CH), 80.6 (C), 71.2 (CH), 68.9 (CH), 56.7 (CH), 45.3 ($CH_2$), 30.9 (CH), 28.4 (3x$CH_3$), 26.6 ($CH_2$), 26.5 ($CH_2$); ***m/z*** (EI) 369 ([M]$^+$, 4 %), 313 (15), 312 ([M-$^t$Bu], 13), 268 ([M-Boc]$^+$, 71), 223 (31), 180 (36), 141 (21), 84 (100).

**(2*RS*,3*SR*,4a*SR*,12c*SR*)-2,3-Dihydroxy-2,3,4,4a,6,12c-hexahydro-1*H*-benzo[*k*]phenanthridine-5-carboxylic acid *tert*-butyl ester 207e ($\Delta^{2,3}$ isomer)**



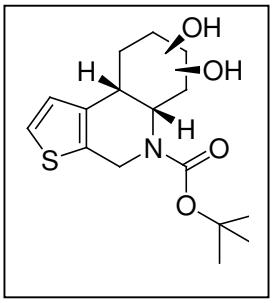

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.52; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3418 (OH), 2927, 1685 (C=O), 1393, 1366, 1163; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 8.11 (1H, d, *J* 8.5, Ar*H*), 7.85 (1H, d, *J* 8.1, Ar*H*), 7.71 (1H, d, *J* 8.3, Ar*H*), 7.55 (1H, t, *J* 8.4, Ar*H*), 7.48 (1H, t, *J* 6.8, Ar*H*), 7.27 (1H, d, *J* 8.3, Ar*H*), 5.10 (1H, d, *J* 16.1, C$H_X$H$_Y$Ar), 4.37 (1H, d, *J* 16.1, CH$_X$$H_Y$Ar), 4.17-4.02 (4H, m, 4xC*H*), 2.71-2.66 (1H, m, C$H_A$H$_B$), 2.44 (1H, br s, O*H*), 2.15-2.10 (2H, m, C$H_2$), 1.86-1.78 (1H, m, CH$_A$$H_B$), 1.60 (1H, br s, O*H*), 1.52 (9H, m, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.9 (C), 135.0 (C), 133.1 (C), 131.9 (C), 130.3 (C), 128.7 (CH), 126.7 (CH), 126.4 (CH), 125.4 (CH), 124.7 (CH), 122.4 (CH), 80.2 (C), 68.5 (CH), 67.9 (CH), 52.3 (CH), 46.6 ($CH_2$), 33.5 ($CH_2$), 31.9 ($CH_2$), 29.9 (CH), 28.5 (3x$CH_3$); ***m/z*** (EI) 369 ([M]$^+$, 4 %), 312 ([M-$^t$Bu]$^+$, 100), 268 ([M-Boc]$^+$, 25), 250 (15), 180 (27).

**(3*RS*,4*SR*,4a*SR*,12c*SR*)-3,4-Dihydroxy-2,3,4,4a,6,12c-hexahydro-1*H*-benzo[*k*]phenanthridine-5-carboxylic acid *tert*-butyl ester 208e ($\Delta^{3,4}$ isomer)**




**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.66; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3409 (OH), 2949, 1662 (C=O), 1393, 1033, 1017; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 8.20 (1H, d, *J* 8.5, Ar*H*), 7.85 (1H, d, *J* 8.1, Ar*H*), 7.76 (1H, d, *J* 8.3, Ar*H*), 7.55 (1H, t, *J* 8.4, Ar*H*), 7.48 (1H, t, *J* 8.1, Ar*H*), 7.33 (1H, d, *J* 8.3, Ar*H*), 5.23 (1H, d, *J* 16.0, C$H_X$$H_Y$Ar), 4.37 (1H, d, *J* 16.0, C$H_X$$H_Y$Ar), 4.18-4.09 (2H, m, 2xC*H*), 4.01-4.00 (1H, m, C*H*), 3.90-3.86 (1H, m, C*H*), 2.52 (1H, br s, O*H*), 2.44-2.35 (1H, m, C$H_A$$H_B$), 2.16-2.04 (1H, m, C$H_A$$H_B$), 1.99-1.93 (1H, m, C$H_C$$H_D$), 1.83-1.79 (1H, m, C$H_C$$H_D$), 1.55 (1H, br s, O*H*), 1.48 (9H, m, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 155.9 (C), 133.3 (2xC), 133.1 (C), 132.0 (C), 128.6 (CH), 127.2 (CH), 126.4 (CH), 125.5 (CH), 125.2 (CH), 123.3 (CH), 80.1 (C), 72.3 (CH), 68.1 (CH), 52.8 (CH), 47.2 ($CH_2$), 37.8 (CH), 28.4 (3x$CH_3$), 25.6 ($CH_2$), 22.8 ($CH_2$); ***m/z*** (EI) 369 ($[M]^+$, 5 %), 313 (26), 312 ($[M-{}^tBu]^+$, 100), 268 ($[M-Boc]^+$, 12), 223 (27), 180 (29).

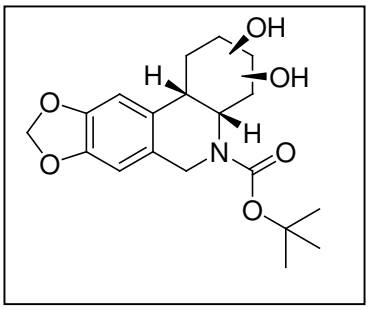
**Dihydroxy-5a,6,7,8,9,9a-hexahydro-4*H*-thieno[2,3-*c*]quinoline-5-carboxylic acid *tert*-butyl ester 206f-208f ($\Delta^{8,9}$, $\Delta^{7,8}$ and $\Delta^{6,7}$ diol mixture)**




General procedure **P** was followed using phenanthridines **195f-197f** (15 mg, 53 µmol), THF (296 µl), $H_2O$ (59 µl), $OsO_4$ (47 µl, 2.5% $^w/_w$ in $^t$BuOH, 3.7 µmol) and NMO (19 mg, 0.158 mmol). Flash chromatography ($CH_2Cl_2$-$CH_2Cl_2$:MeOH, 100:5) afforded mixture of diols **206f-208f** (10 mg, 64%) as a yellow oil.

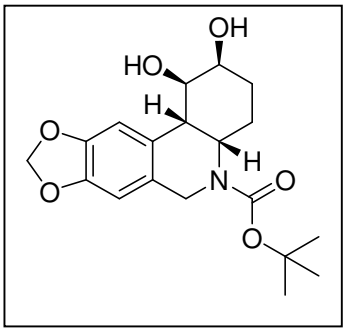
**$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3421 (OH), 2929, 1676 (C=O), 1410, 1365, 1165; ***m/z*** (EI) 325 ($[M]^+$, 1 %), 268 ($[M-{}^tBu]^+$, 73), 224 (18), 152 (14).

**Dihydroxy-2,3,4,4a,6,11b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid *tert*-butyl ester 206k-208k**



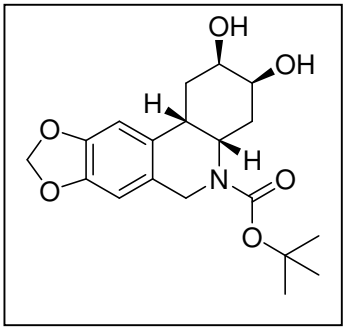
General procedure **P** was followed using phenanthridines **195k**-**197k** (125 mg, 0.38 mmol), THF (2.66 ml), $H_2O$ (531 µl), $OsO_4$ (332 µl, 2.5% $^{w}/_{w}$ in $^{t}$BuOH, 26.6 µmol) and NMO (133 mg, 1.14 mmol). Flash chromatography ($CH_2Cl_2$:MeOH, 98:2) afforded $\Delta^{1,2}$ diol **206k** (13 mg, 9%), $\Delta^{2,3}$ diol **207k** (31 mg, 23%), $\Delta^{3,4}$ diol **208k** (25 mg, 18%), minor diastereomer **209k** (3 mg, 2%) and mixed diol (48 mg, 35%) giving a total yield (120 mg, 87%).

**(1R,2S,4a*SR*,11b*SR*)-1,2-Dihydroxy-2,3,4,4a,6,11b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid *tert*-butyl ester 206k ($\Delta^{1,2}$ isomer)**



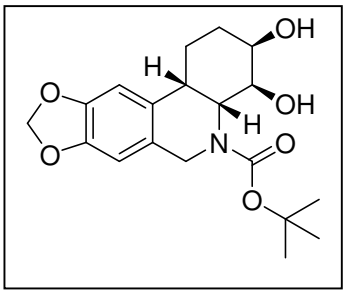
**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.52; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3392 (OH), 1685 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.83 (1H, s, Ar*H*), 6.61 (1H, s, Ar*H*), 5.94 (2H, dd, *J* 3.2, 1.4, O$CH_2$O), 4.66-4.59 (3H, m, 2xC*H*OH+C$H_X$H$_Y$Ar), 4.24 (1H, d, *J* 16.8, C$H_X$$H_Y$*Ar*), 3.75-3.71 (1H, m, C*H*), 3.20 (1H, br s, C*H*), 2.41 (1H, br s, OH), 2.10-1.83 (3H, m, O*H*+$CH_2$), 1.70-1.61 (2H, m, $CH_2$), 1.52 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.8 (C), 147.0 (C), 146.2 (C), 126.8 (C), 126.1 (C), 106.7 (CH), 105.7 (CH), 100.9 ($CH_2$), 79.9 (C), 71.4 (CH), 67.4 (CH), 47.2 (CH), 43.6 ($CH_2$), 42.8 (CH), 28.9 (3x$CH_3$), 27.3 ($CH_2$), 24.0 ($CH_2$); ***m/z*** (EI) 363 ([M]$^+$, 6 %), 306 (53), 252 (22), 224 (30).

**(2R,3S,4a*SR*,11b*SR*)-2,3-Dihydroxy-2,3,4,4a,6,11b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid *tert*-butyl ester 207k ($\Delta^{2,3}$ isomer)**



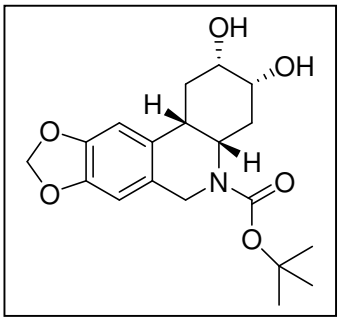
**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.59; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3391 (OH), 2931, 1684 (C=O), 1241, 1165; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.94 (1H, s, Ar*H*), 6.58 (1H, s, Ar*H*), 5.93-5.91 (2H, m, O$CH_2$O), 4.72-4.65 (1H, m, C*H*), 4.59 (1H, d, *J* 16.9, $CH_XH_YAr$), 3.93 (1H, d, *J* 2.7, C*H*), 3.65-3.61 (1H, m, C*H*), 3.16 (1H, br s, C*H*), 2.35-2.30 (1H, m, $CH_AH_B$), 2.26-2.19 (1H, m, $CH_AH_B$), 1.90-1.86 (1H, m, $CH_CH_D$), 1.56-1.50 (10H, m, $CH_CH_D$+3x$CH_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.7 (C), 147.0 (C), 146.2 (C), 127.7 (C), 126.3 (C), 106.4 (CH), 105.8 (CH), 100.8 ($CH_2$), 80.0 (C), 69.4 (CH), 66.7 (CH), 46.3 (CH), 43.6 ($CH_2$), 36.2 (CH), 31.3 ($CH_2$), 29.7 ($CH_2$), 28.4 (3x$CH_3$); ***m/z*** (EI) 363 ([M]$^+$, 1 %), 306 (12), 263 (18), 262 (100), 218 (12), 174 (23).

**(3R,4S,4a*SR*,11b*SR*)-3,4-Dihydroxy-2,3,4,4a,6,11b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid *tert*-butyl ester 208k ($\Delta^{3,4}$ isomer)**



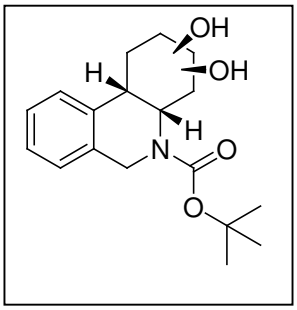
**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.62; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3391 (OH), 2924, 1684 (C=O), 1240, 1164; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.80 (1H, s, Ar*H*), 6.60 (1H, s, Ar*H*), 5.93 (2H, dd, *J* 5.0, 1.3, O$CH_2$O), 4.67-4.55 (2H, m, C*H*+$CH_XH_Y$Ar), 4.32 (1H, d, *J* 16.1, $CH_XH_YAr$), 3.95 (1H, d, *J* 2.5, C*H*), 3.34 (1H, br d, *J* 9.6, C*H*), 3.17 (1H, br s, C*H*), 2.61 (1H, br s, O*H*), 2.30-2.20 (1H, m, $CH_AH_B$), 2.13-2.05 (1H, m, $CH_AH_B$), 1.81 (1H, dd, *J* 14.4, 3.0, $CH_CH_D$), 1.60-1.45 (11H, m, O*H*+$CH_CH_D$+3x$CH_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 157.2 (C), 150.0 (C), 146.1 (C), 128.0 (C), 126.4 (C), 106.6 (CH), 105.6 (CH), 100.9 ($CH_2$), 80.8 (C), 69.6 (2xCH), 53.0 (CH), 44.2 ($CH_2$), 36.7 (CH), 28.4 (3x$CH_3$), 25.4 ($CH_2$), 20.5 ($CH_2$); ***m/z*** (EI) 363 ([M]$^+$, 2 %), 308 (22), 262 (100), 244 (7), 218 (12), 174 (13), 135 (23).

**(2*S*,3*R*,4a*SR*,11b*SR*)-2,3-Dihydroxy-2,3,4,4a,6,11b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic acid *tert*-butyl ester 209k ($\Delta^{2,3}$ isomer, minor diastereomer)**



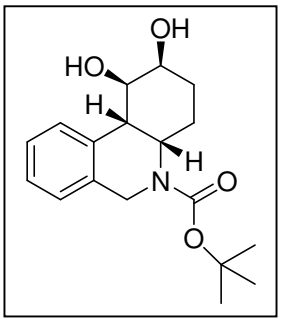
**$R_f$** [$CH_2Cl_2$:MeOH, 95:5] = 0.37; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3421 (OH), 2925, 1684 (C=O), 1236, 1165; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 6.99 (1H, s, Ar*H*), 6.57 (1H, s, Ar*H*), 5.93 (2H, s, OC$H_2$O), 4.71 (1H, d, *J* 17.1, $CH_XH_YAr$), 4.38-4.32 (1H, m, C*H*), 4.27 (1H, d, *J* 16.7, $CH_XH_YAr$), 3.96 (1H, br s, C*H*), 3.71 (1H, br s, C*H*), 3.07 (1H, br s, C*H*), 2.76 (1H, dt, *J* 15.5, 3.3, $CH_AH_B$), 2.02-2.00 (1H, m, $CH_AH_B$), 1.80-1.72 (2H, m, C$H_2$), 1.51 (9H, s, 3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.5 (C), 146.7 (C), 146.3 (C), 128.5 (C), 125.7 (C), 106.9 (CH), 106.3 (CH), 100.9 ($CH_2$), 80.1 (C), 70.5 (CH), 69.0 (CH), 49.7 (CH), 43.2 ($CH_2$), 33.7 (CH), 30.8 ($CH_2$), 29.4 ($CH_2$), 28.4 (3x$CH_3$); ***m/z*** (EI) 364 ($[M+H]^+$, 5 %), 363 ($[M]^+$, 2), 306 (16), 262 (100), 218 (16).

**Dihydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206m-207m**



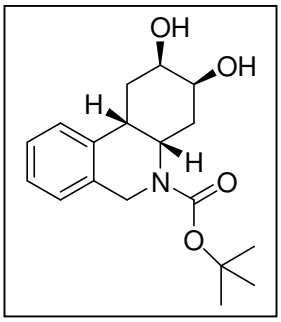
General procedure **P** was followed using phenanthridines **96b-98b** (200 mg, 0.70 mmol), THF (3.92 ml), $H_2O$ (785 µl), $OsO_4$ (613 µl, 2.5% $^w/_w$ in $^t$BuOH, 49.1 µmol) and NMO (329 mg, 2.81 mmol). Flash chromatography ($CH_2Cl_2$-$CH_2Cl_2$:MeOH, 100:3) afforded mixture of diols **206m-208m** as a colourless oil (156 mg, 70%). HPLC (EtOAc:hexane, 3:1) of this mixture afforded $\Delta^{1,2}$ diol **206m** (29 mg, 13%), $\Delta^{2,3}$ diol **207m** (25 mg, 11%), $\Delta^{3,4}$ diol **208m** (26 mg, 12%), and mixed diol fractions (44 mg, 20%), giving an overall yield (124 mg, 56%), all colourless oils.

**(1*RS*,2*SR*,4a*SR*,10b*SR*)-1,2-Dihydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 206m ($\Delta^{1,2}$ isomer)**



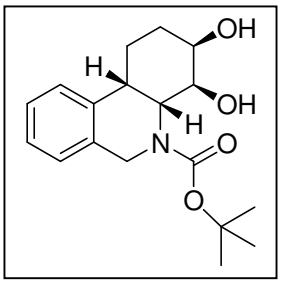

**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.57; **$R_t$** (EtOAc:hexane, 3:1, flow rate: 8 ml/min) = 23 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3421 (OH), 1664 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.36-7.34 (1H, m, Ar*H*), 7.24-7.18 (2H, m, 2xAr*H*), 7.14-7.12 (1H, m, Ar*H*), 4.74-4.66 (3H, m, C*H*OH+C*H*NBoc+C$H_X$H$_Y$Ar), 4.35 (1H, d, *J* 17.1, CH$_X$$H_Y$Ar), 3.95 (1H, br s, O*H*), 3.71 (1H, ddd, *J* 11.4, 4.7, 2.8, C*H*OH), 3.40 (1H, br s, C*H*Ar), 1.95-1.85 (1H, m, C$H_A$H$_B$), 1.70-1.60 (2H, m, CH$_A$$H_B$+C$H_C$H$_D$), 1.51 (9H, s, 3xC$H_3$), 1.40-1.33 (1H, m, CH$_C$$H_D$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.9 (C), 133.4 (C), 133.1 (C), 126.9 (CH), 126.6 (C), 126.3 (CH), 125.4 (CH), 79.9 (C), 71.1 (CH), 67.4 (CH), 47.1 (CH), 43.6 ($CH_2$), 42.8 (CH), 28.4 (3x$CH_3$), 27.4 ($CH_2$), 24.2 ($CH_2$); ***m/z*** (EI) 319 ([M]$^+$, 2 %), 262 ([M-$^t$Bu]$^+$, 100), 218 ([M-Boc]$^+$, 22), 184 (75). This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

**(2*RS*,3*SR*,4a*SR*,10b*SR*)-2,3-Dihydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 207m ($\Delta^{2,3}$ isomer)**




**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.52; **$R_t$** (EtOAc:hexane, 3:1, flow rate: 8 ml/min) = 28 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3414 (OH), 2930, 1671 (C=O), 1406, 1365; **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.47 (1H, d, *J* 7.6, Ar*H*), 7.27-7.20 (2H, m, 2xAr*H*), 7.12 (1H, d, *J* 6.8, Ar*H*), 4.78-4.72 (1H, m, C*H*NBoc), 4.71 (1H, d, *J* 17.3, C$H_X$H$_Y$Ar), 4.36 (1H, d, *J* 17.3, CH$_X$$H_Y$*Ar*), 3.92 (1H, m, C*H*OH), 3.64 (1H, dt, *J* 12.0, 3.9, C*H*OH), 3.26 (1H, br s, C*H*Ar), 2.49 (1H, dt, *J* 13.6, 3.1, C$H_A$H$_B$), 2.25 (1H, ddd, *J* 13.6, 12.0, 4.8, CH$_A$$H_B$), 1.94-1.87 (1H, m, C$H_C$H$_D$), 1.54-1.45 (10H, m, CH$_C$$H_D$+3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 154.8 (C), 134.5 (C), 133.2 (C), 126.9 (CH), 126.4 (CH), 126.2 (CH), 125.6 (CH), 80.0 (C), 69.4 (CH), 66.7 (CH), 46.3 (CH), 43.6 ($CH_2$), 36.3 (CH), 31.5 ($CH_2$), 29.3 ($CH_2$), 28.4 (3x$CH_3$); ***m/z*** (EI) 319 ([M]$^+$, 1 %), 263 ([M-$^t$Bu]$^+$, 27), 262 (80), 218 ([M-Boc]$^+$, 25), 200 (27), 174 (36), 146 (25), 144 (48); **HRMS** (EI) Found: [M]$^+$, 319.1780. $C_{18}H_{25}O_4N$ requires 319.1778.

**(3*RS*,4*SR*,4a*RS*,10b*SR*)-3,4-Dihydroxy-2,3,4,4a,6,10b-hexahydro-1*H*-phenanthridine-5-carboxylic acid *tert*-butyl ester 208m ($\Delta^{3,4}$ isomer)**

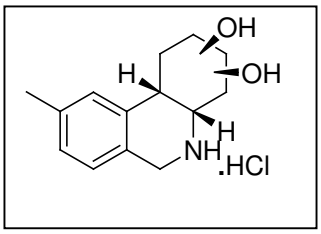



**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.58; **$R_t$** (EtOAc:hexane, 3:1, flow rate: 8 ml/min) = 21 min; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3394 (OH), 2978, 2937, 1668 (C=O); **$^1$H NMR** δ (360 MHz, 323 K, $CDCl_3$) 7.33 (1H, d, *J* 7.5, Ar*H*), 7.27-7.19 (2H, m, 2xAr*H*), 7.14 (1H, d, *J* 7.1, Ar*H*), 4.80-4.66 (2H, m, C*H*NBoc+C$H_X$H$_Y$Ar), 4.44 (1H, d, *J* 17.0, CH$_X$$H_Y$Ar), 3.94 (1H, dd, *J* 5.9, 2.9, C*H*OH), 3.31-3.29 (2H, m, C*H*Ar+C*H*OH), 2.29-2.24 (2H, m, C$H_2$), 1.85-1.80 (1H, m, C$H_A$H$_B$), 1.58-1.52 (10H, m, CH$_A$$H_B$+3xC$H_3$); **$^{13}$C NMR** δ (90.6 MHz, 323 K, $CDCl_3$) 156.7 (C), 134.6 (C), 133.3 (C), 126.9 (CH), 126.5 (CH), 126.2 (CH), 125.3 (CH), 80.8 (C), 69.6 (2xCH), 53.1 (CH), 43.9 ($CH_2$), 36.9 (CH), 28.4 (3x$CH_3$), 25.4 ($CH_2$), 20.0 ($CH_2$); ***m/z*** (EI) 319 ([M]$^+$, 1 %), 263 ([M-$^t$Bu], 3), 233 (7), 218 ([M-Boc]$^+$, 6). This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

**General procedure Q – Hydrochloride salt formation**

To a solution of the appropriate diol(s) **206-208** in $CH_2Cl_2$ (2 ml) was added TFA (5 ml) and the reaction was stirred at r.t. for 2 h. The reaction was diluted with $H_2O$ (15 ml), adjusted to pH 8-9 by the addition of NaOH pellets, and then extracted with $CH_2Cl_2$ (3 x 15 ml). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. The resultant oil was taken up in $CH_2Cl_2$ (1 ml), cooled to 0 $^o$C and HCl (excess, 1 M in $Et_2O$) added. The resultant solid was washed with $Et_2O$ and dried under vacuum to afford the desired amine hydrochloride(s) **252-254**.

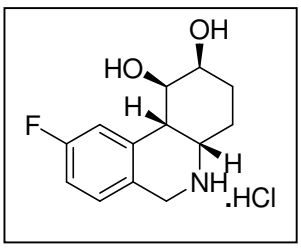
**9-Methyl-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-diol hydrochloride 252a-254a ($\Delta^{1,2}$, $\Delta^{2,3}$, $\Delta^{3,4}$ isomer mixture)**




General procedure **Q** was followed using diols **206a-208a** (16 mg, 48 µmol), $CH_2Cl_2$ (2 ml) and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford a amine hydrochlorides **252a-254a** as a yellow oil (9 mg, 69%).

***m/z*** (ESI+) 234 ($[M+H]^+$, 100 %), 232 (44); **HRMS** (ESI+) Found $[M+H]^+$, 234.1489. $C_{14}H_{20}O_2N$ requires 234.1489.

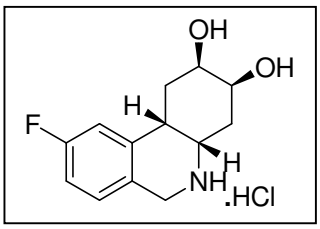
**(1*RS*,2*SR*,4a*SR*,10b*SR*)-9-Fluoro-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-1,2-diol 252b ($\Delta^{1,2}$ isomer)**




General procedure **Q** was followed using diol **206b** (10 mg, 30 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **252b** as a colourless oil (9 mg, 99%).

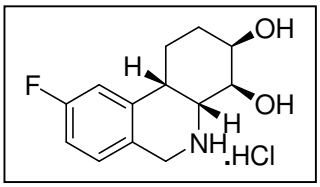
**$^1$H NMR** δ (360 MHz, $D_2O$) 7.09 (1H, dd, *J* 8.6, 5.7, Ar*H*), 7.03 (1H, dd, *J* 10.2, 2.6, Ar*H*), 6.94 (1H, td, *J* 8.6, 2.7, ArH), 4.28 (1H, d, *J* 16.2, C$H_X$H$_Y$Ar), 4.22 (1H, d, *J* 16.2, CH$_X$$H_Y$Ar), 3.88 (1H, d, *J* 7.6, C*H*), 3.78-3.74 (2H, m, 2xC*H*), 3.19 (1H, dd, *J* 8.2, 4.4, C*H*), 2.01-1.91 (1H, m, C$H_A$H$_B$), 1.81-1.72 (1H, m,CH$_A$$H_B$), 1.68-1.60 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $D_2O$) 162.3 (1C, d, *J* 243.8, C), 135.0 (1C, d, *J* 7.7, C), 129.2 (1C, d, *J* 8.5, CH), 123.7 (C), 116.4 (1C, d, *J* 23.7, CH), 115.5 (1C, d, *J* 22.1, CH), 70.9 (CH), 68.2 (CH), 52.0 (CH), 43.4 ($CH_2$), 39.5 (CH), 25.6 ($CH_2$), 21.9 ($CH_2$); ***m/z*** (ESI+) 238 ($[M+H]^+$, 100 %), 236 (86); **HRMS** (ESI+) Found $[M+H]^+$, 238.1237. $C_{13}H_{17}O_2NF$ requires 238.1238.

**(2*RS*,3*SR*,4a*SR*,10b*SR*)-Fluoro-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-2,3-diol 253b ($\Delta^{2,3}$ isomer)**



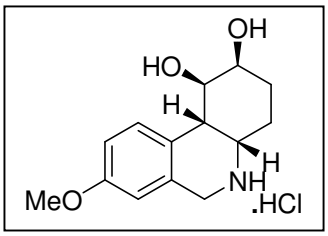

General procedure **Q** was followed using diol **207b** (10 mg, 30 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **253b** as a colourless oil (7 mg, 86%). **$^1$H NMR** δ (360 MHz, $D_2O$) 7.09-7.05 (1H, m, Ar*H*), 6.98 (1H, dd, *J* 10.0, 2.1, Ar*H*), 6.91 (1H, td, *J* 8.7, 2.6, ArH), 4.23 (1H, s, C$H_2$Ar), 3.81 (1H, dd, *J* 9.8, 4.7, C*H*), 3.77-3.75 (2H, m, 2xC*H*), 3.27-3.23 (1H, m, C*H*), 2.10-2.00 (2H, m, C$H_2$), 1.87-1.80 (1H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $D_2O$) 162.7 (1C, d, *J* 244.5, C), 137.2 (1C, d, *J* 7.6, C), 129.0 (1C, d, *J* 8.5, CH), 122.8 (C), 115.0 (1C, d, *J* 22.4, CH), 114.8 (1C, d, *J* 22.9, CH), 67.6 (CH), 66.5 (CH), 51.7 (CH), 43.9 ($CH_2$), 33.2 ($CH_2$), 31.6 (CH), 29.0 ($CH_2$); ***m/z*** (ESI+) 238 ($[M+H]^+$, 100 %), 211 (12), 179 (12); **HRMS** (ESI+) Found $[M+H]^+$, 238.1234. $C_{13}H_{17}O_2NF$ requires 238.1238.

**(3*RS*,4*SR*,4a*RS*,10b*SR*)-9-Fluoro-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-3,4-diol 254b ($\Delta^{3,4}$ isomer)**




General procedure **Q** was followed using diol **208b** (15 mg, 46 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **254b** as a yellow oil (9 mg, 74%). **$^1$H NMR** δ (360 MHz, $D_2O$) 7.11-7.05 (2H, m, 2xAr*H*), 6.91 (1H, dd, *J* 8.6, 2.7, Ar*H*), 4.23 (1H, d, *J* 16.3, C$H_X$H$_Y$Ar), 4.17 (1H, d, *J* 16.3, CH$_X$$H_Y$Ar), 3.84-3.82 (1H, m6, C*H*), 3.77 (1H, dd, *J* 9.5, 5.3, C*H*), 3.59-3.57 (1H, m, C*H*), 3.32-3.30 (1H, m, C*H*), 2.02-1.92 (2H, m, C$H_2$), 1.64-1.57 (1H, m, C$H_A$H$_B$), 1.39-1.31 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (90.6 MHz, $D_2O$) 163.1 (1C, d, *J* 245.1, C), 136.3 (C), 129.8 (1C, d, *J* 8.7, CH), 124.6 (C), 115.1 (1C, d, *J* 22.2, CH), 113.9 (1C, d, *J* 23.3, CH), 69.5 (CH), 66.7 (CH), 54.6 (CH), 49.5 ($CH_2$), 34.3 (CH), 26.3 ($CH_2$), 21.9 ($CH_2$); ***m/z*** (ESI+) 238 ($[M+H]^+$, 100 %), 225 (18), 211 (26), 210 (10), 197 (13), 179 (26); **HRMS** (ESI+) Found $[M+H]^+$, 238.1233. $C_{13}H_{17}O_2NF$ requires 238.1238.

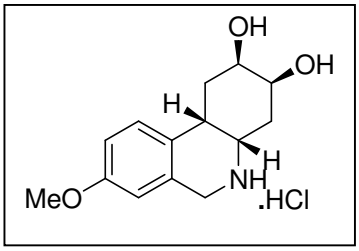
**(1*RS*,2*SR*,4a*SR*,10b*SR*)-8-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-1,2-diol 252c ($\Delta^{1,2}$ isomer)**




General procedure **Q** was followed using diol **206c** (21 mg, 60 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **252c** as a colourless oil (14 mg, 82%).

**$^1$H NMR** δ (800 MHz, $D_2O$) 7.17 (1H, d, *J* 8.8, Ar*H*), 6.76 (1H, d, *J* 8.8, 2.4, Ar*H*), 6.64 (1H, d, *J* 1.6, Ar*H*), 4.23 (1H, d, *J* 16.6, C$H_X$H$_Y$Ar), 4.18 (1H, d, *J* 16.6, CH$_X$$H_Y$Ar), 3.85 (1H, br s, C*H*), 3.72-3.66 (2H, m, 2xC*H*), 3.61 (3H, s, C$H_3$), 3.12 (1H, m, C*H*), 1.92-1.89 (1H, m, C$H_A$H$_B$), 1.73-1.70 (1H, m, CH$_A$$H_B$), 1.63-1.52 (2H, m, C$H_2$); **$^{13}$C NMR** δ (200.0 MHz, $D_2O$) 158.6 (C), 131.1 (CH), 129.0 (C), 124.9 (C), 114.7 (CH), 111.9 (CH), 71.1 (CH), 68.1 (CH), 56.0 ($CH_3$), 52.2 (CH), 43.4 ($CH_2$), 38.7 (CH), 25.5 ($CH_2$), 21.8 ($CH_2$); ***m/z*** (ESI+) 250 ($[M+H]^+$, 100 %), 248 (86), 246 (13); **HRMS** (ESI+) Found $[M+H]^+$, 250.1435. $C_{14}H_{20}O_3N$ requires 250.1438.

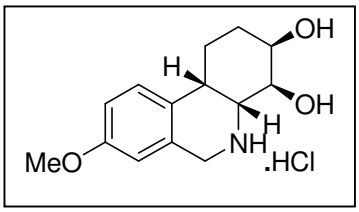
**(2*RS*,3*SR*,4a*SR*,10b*SR*)-8-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-2,3-diol 253b ($\Delta^{2,3}$ isomer)**




General procedure **Q** was followed using diol **207b** (20 mg, 57 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **253c** as a yellow oil (15 mg, 92%).

**$^1$H NMR** δ (360 MHz, $D_2O$) 7.12 (1H, d, *J* 8.7, Ar*H*), 6.79 (1H, dd, *J* 8.5, 2.2, Ar*H*), 6.62 (1H, br s, Ar*H*), 4.23-4.14 (2H, m, C$H_2$Ar), 3.75-3.64 (3H, m, 3xC*H*), 3.60 (3H, s, OC$H_3$), 3.18-3.13 (1H, m, C*H*), 2.06-1.94 (2H, m, C$H_2$), 1.85-1.72 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $D_2O$) 158.1 (C), 129.8 (CH), 128.3 (C), 127.3 (C), 115.2 (CH), 111.5 (CH), 67.6 (CH), 66.4 (CH), 55.7 ($CH_3$), 52.3 (CH), 44.2 ($CH_2$), 32.4 ($CH_2$), 30.5 (CH), 29.0 ($CH_2$); ***m/z*** (ESI+) 250 ($[M+H]^+$, 100 %), 249 (28), 248 (89); **HRMS** (ESI+) Found $[M+H]^+$, 250.1438. $C_{14}H_{20}O_3N$ requires 250.1438.

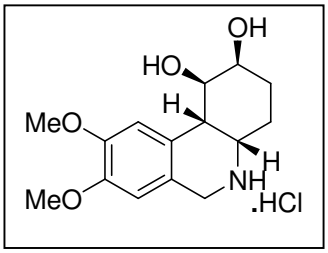
**(3*RS*,4*SR*,4a*RS*,10b*SR*)-8-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-3,4-diol 254c ($\Delta^{3,4}$ isomer)**




General procedure **Q** was followed using diol **208c** (2.1 mg, 6 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **254c** as a colourless oil (1.4 mg, 94%).

**$^1$H NMR** δ (800 MHz, $D_2O$) 7.22 (1H, d, *J* 8.0, Ar*H*), 6.82 (1H, dd, *J* 8.8, 3.2, Ar*H*), 6.67 (1H, d, *J* 2.4, Ar*H*), 4.20 (1H, d, *J* 16.8, C$H_X$H$_Y$Ar), 4.15 (1H, d, *J* 16.8, CH$_X$$H_Y$Ar), 3.80 (1H, br s, C*H*), 3.70 (1H, m, C*H*), 3.64 (3H, s, C$H_3$), 3.60 (1H, m, C*H*), 3.23 (1H, br s, C*H*), 1.90-1.86 (2H, m, C$H_2$), 1.59-1.56 (1H, m, C$H_A$H$_B$), 1.35-1.31 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (90.6 MHz, $D_2O$) 158.0 (C), 130.9 (CH), 130.0 (C), 128.6 (C), 114.9 (CH), 111.8 (CH), 70.1 (CH), 69.1 (CH), 55.8 ($CH_3$), 54.7 (CH), 41.6 ($CH_2$), 33.2 (CH), 26.9 ($CH_2$), 26.0 ($CH_2$); ***m/z*** (ESI+) 250 ($[M+H]^+$, 100 %), 248 (73), 239 (17), 233 (10), 211 (17), 209 (25), 197 (27), 185 (26); **HRMS** (ESI+) Found $[M+H]^+$, 250.1436. $C_{14}H_{20}O_3N$ requires 250.1438.

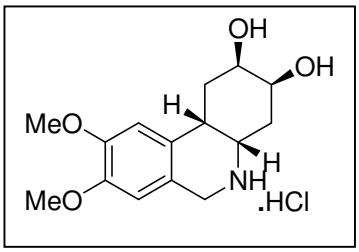
**(1*RS*,2*SR*,4a*SR*,10b*SR*)-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-1,2-diol hydrochloride 252d ($\Delta^{1,2}$ isomer)**




General procedure **Q** was followed using diol **206d** (10 mg, 26 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **252d** as a yellow oil (9 mg, 88%).

**$^1$H NMR** δ (250 MHz, $D_2O$) 6.82 (1H, s, Ar*H*), 6.68 (1H, s, Ar*H*), 4.18 (2H, br s, C$H_2$Ar), 3.83-3.80 (1H, m, C*H*), 3.75-3.68 (2H, m, 2xC*H*), 3.66 (3H, s, C$H_3$), 3.64 (3H, s, C$H_3$), 3.09 (1H, q, *J* 4.4, C*H*), 2.04-1.87 (1H, m, C$H_A$H$_B$), 1.79-1.52 (3H, m, C$H_2$+CH$_A$$H_B$); **$^{13}$C NMR** δ (62.9 MHz, $D_2O$) 148.1 (C), 147.8 (C), 125.2 (C), 120.0 (C), 112.8 (CH), 109.9 (CH), 71.1 (CH), 68.1 (CH), 56.2 (2x$CH_3$), 52.2 (CH), 43.2 ($CH_2$), 38.5 (CH), 25.3 ($CH_2$), 21.6 ($CH_2$); ***m/z*** (ESI+) 280 ($[M+H]^+$, 61 %), 279 ($[M]^+$, 100); **HRMS** (ESI+) Found $[M+H]^+$, 280.1542. $C_{15}H_{22}O_4N$ requires 280.1543.

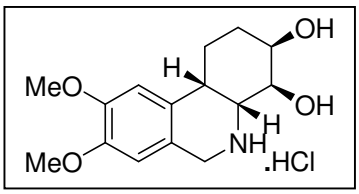
**(2*RS*,3*SR*,4a*SR*,10b*SR*)-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-2,3-diol hydrochloride 253d ($\Delta^{2,3}$ isomer)**




General procedure **Q** was followed using diols **206d** and **207d** (6.2 mg, 16 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochlorides **252d** and **253d** as a yellow oil (3 mg, 60%). Data for $\Delta^{2,3}$ isomer **253d** was deduced from $^1H$, $^{13}C$ and HSQC NMR data for the mixture of **252d** and **253d**.

**$^1$H NMR** δ (500 MHz, $D_2O$) 6.76 (1H, s, Ar*H*), 6.66 (1H, s, Ar*H*), 4.18-4.15 (2H, m, C$H_2$Ar), 3.75-3.71 (3H, m, 3xC*H*), 3.67 (3H, s, OC$H_3$), 3.64 (3H, s, OC$H_3$), 3.18-3.15 (1H, m, C*H*), 2.07-2.028 (2H, m, C$H_A$H$_{B+}$C$H_C$H$_D$), 1.92-1.88 (1H, m, CH$_A$$H_B$), 1.83-1.78 (1H, m, CH$_C$$H_D$); **$^{13}$C NMR** δ (125.8 MHz, $D_2O$) 147.9 (C), 147.6 (C), 125.2 (C), 119.8 (C), 112.7 (CH), 111.1 (CH), 70.9 (CH), 67.5 (CH), 55.9 (2xCH$_3$), 53.3 (CH), 43.9 (CH$_2$), 33.6 (CH), 30.7 (CH$_2$), 28.9 (CH$_2$); ***m/z*** (ESI+) 280 ([M+H]$^+$, 100 %), 262 (6); **HRMS** (ESI+) Found [M+H]$^+$, 280.1542. $C_{15}H_{22}O_4N$ requires 280.1543.

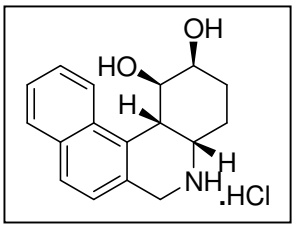
**(3*RS*,4*SR*,4a*RS*,10b*SR*)-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-3,4-diol hydrochloride 254d ($\Delta^{3,4}$ isomer)**




General procedure **Q** was followed using diol **208d** (10 mg, 26 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **254d** as a yellow oil (5 mg, 60%).

**$^1$H NMR** δ (360 MHz, $D_2O$) 6.82 (1H, s, Ar*H*), 6.67 (1H, s, Ar*H*), 4.16 (1H, d, *J* 16.1, C$H_X$H$_Y$Ar), 4.09 (1H, d, *J* 16.1, CH$_X$$H_Y$Ar), 3.78 (1H, br s, C*H*), 3.72-3.65 (1H, m, C*H*), 3.65 (3H, s, OC$H_3$), 3.62 (3H, s, OC$H_3$), 3.23 (1H, br s, C*H*), 2.00-1.89 (2H, m, C$H_2$), 1.64-1.53 (1H, m, C$H_A$H$_B$), 1.38-1.29 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (90.6MHz, $D_2O$) 148.6 (C), 147.6 (C), 126.3 (C), 120.7 (C), 110.0 (2xCH), 71.7 (CH), 69.1 (CH), 56.1 (2xCH$_3$), 54.6 (CH), 41.0 (CH$_2$), 33.4 (CH), 26.0 (CH$_2$), 21.6 (CH$_2$); ***m/z*** (ESI+) 280 ([M+H]$^+$, 100 %); **HRMS** (ESI+) Found [M+H]$^+$, 280.1546. $C_{15}H_{22}O_4N$ requires 280.1543.

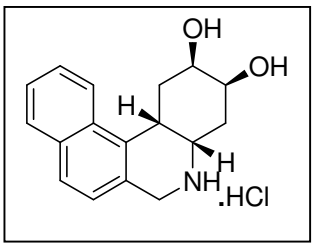
**(1*RS*,2*SR*,4a*SR*,12c*SR*)-1,2,3,4,4a,5,6,12c-Octahydro-benzo[*k*]phenanthridine-1,2-diol hydrochloride 252e ($\Delta^{1,2}$ isomer)**




General procedure **Q** was followed using diol **206e** (20 mg, 54 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **252e** as a colourless oil (11 mg, 67%).

**$^1$H NMR** δ (500 MHz, $D_2O$) 8.09 (1H, d, *J* 8.5, Ar*H*), 7.77 (1H, d, *J* 6.5, Ar*H*), 7.76 (1H, d, *J* 9.0, Ar*H*), 7.48-7.41 (2H, m, 2xAr*H*), 7.19 (1H, d, *J* 8.5, Ar*H*), 4.52 (1H, d, *J* 16.5, C$H_X$H$_Y$Ar), 4.44 (1H, d, *J* 16.5, C$H_X$H$_Y$Ar), 4.05 (2H, s, 2xC*H*), 3.65 (2H, s, 2xC*H*), 2.22-2.16 (1H, m, C$H_A$H$_B$), 1.92-1.89 (1H, m, CH$_A$$H_B$), 1.81 (2H, d, *J* 2.5, C$H_2$); **$^{13}$C NMR** δ (125.9 MHz, $D_2O$) 135.0 (C), 134.7 (C), 132.6 (C), 130.8 (CH), 130.7 (CH), 128.7 (2xCH), 127.7 (C), 127.3 (CH), 126.5 (CH), 74.7 (CH), 71.3 (CH), 56.0 (CH), 46.9 ($CH_2$), 35.7 (CH), 27.8 ($CH_2$), 24.2 ($CH_2$); ***m/z*** (ESI+) 270 ([M+H]$^+$, 38 %), 261 (13), 260 (15), 239 (36), 217 (15), 192 (22), 191 (44), 168 (100); **HRMS** (ESI+) Found [M+H]$^+$, 270.1488. $C_{17}H_{20}O_4N$ requires 270.1489.

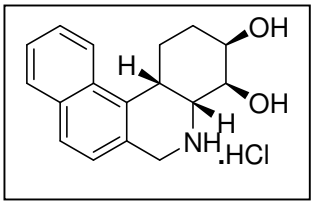
**(2*RS*,3*SR*,4a*SR*,12c*SR*)-1,2,3,4,4a,5,6,12c-Octahydro-benzo[*k*]phenanthridine-2,3-diol hydrochloride 253e ($\Delta^{2,3}$ isomer)**




General procedure **Q** was followed using diol **207e** (40 mg, 66 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **253e** as a colourless oil (20 mg, 61%).

**$^1$H NMR** δ (360 MHz, $D_2O$) 7.85 (1H, d, *J* 8.4, Ar*H*), 7.78 (1H, d, *J* 8.2, Ar*H*), 7.68 (1H, d, *J* 8.6, Ar*H*), 7.51 (1H, t, *J* 7.0, Ar*H*), 7.43 (1H, t, *J* 7.0, Ar*H*), 7.09 (1H, d, *J* 8.6, Ar*H*), 4.37 (2H, s, C$H_2$Ar), 3.95 (1H, br s, C*H*), 3.81-3.76 (2H, m, 2xC*H*), 3.67 (1H, br s, C*H*), 2.33-2.17 (2H, m, C$H_2$), 2.94-1.97 (1H, m, C$H_A$H$_B$), 1.67-1.52 (1H, m, CH$_A$$H_B$); **$^{13}$C NMR** δ (62.9 MHz, $D_2O$) 133.9 (C), 131.8 (C), 130.9 (C), 130.0 (CH), 129.1 (CH), 128.4 (CH), 127.6 (CH), 125.1 (CH), 125.0 (C), 123.7 (CH), 69.1 (CH), 66.5 (CH), 54.5 (CH), 46.5 ($CH_2$), 34.3 (CH), 30.5 ($CH_2$), 28.1 ($CH_2$); ***m/z*** (ESI+) 270 ([M+H]$^+$, 100 %), 232 (15), 231 (12), 217 (16), 203 (16); **HRMS** (ESI+) Found [M+H]$^+$, 270.1481. $C_{17}H_{20}O_2N$ requires 270.1489.

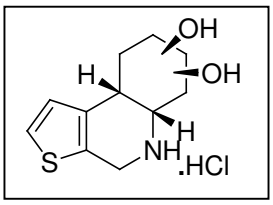
**(3*RS*,4*SR*,4a*RS*,12c*SR*)-1,2,3,4,4a,5,6,12c-Octahydro-benzo[*k*]phenanthridine-3,4-diol hydrochloride 254e ($\Delta^{3,4}$ isomer)**




General procedure **Q** was followed using diol **208e** (23 mg, 63 µmol), $CH_2Cl_2$ (2 ml), and TFA (5 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **254e** as a colourless oil (13 mg, 69%).

**$^1$H NMR** δ (360 MHz, $D_2O$) 8.05 (1H, d, *J* 7.5, Ar*H*), 7.77-7.73 (2H, m, 2xAr*H*), 7.46-7.41 (2H, m, 2xAr*H*), 7.16 (1H, d, *J* 8.5, Ar*H*), 4.52 (1H, d, *J* 16.5, C$H_X$H$_Y$Ar), 4.39 (1H, d, *J* 16.5, C$H_X$H$_Y$Ar), 4.04-3.95 (2H, s, 2xC*H*), 3.64 (1H, d, *J* 11.4, C*H*), 3.54 (1H, br s, CH), 2.22-2.13 (1H, m, C$H_A$H$_B$), 1.93-1.89 (1H, m, CH$_A$$H_B$), 1.81-1.77 (2H, m, C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $D_2O$) 133.5 (C), 133.2 (C), 130.9 (C), 129.3 (CH), 129.2 (CH), 127.3 (2xCH), 125.9 (CH), 125.7 (C), 125.0 (CH), 73.1 (CH), 69.6 (CH), 54.5 (CH), 45.2 ($CH_2$), 34.0 (CH), 26.2 ($CH_2$), 22.6 ($CH_2$); ***m/z*** (ESI+) 270 ([M+H]$^+$, 71 %), 248 (12), 245 (14), 234 (15), 217 (21), 203 (16), 172 (27); **HRMS** (ESI+) Found [M+H]$^+$, 270.1481. $C_{17}H_{20}O_2N$ requires 270.1489.

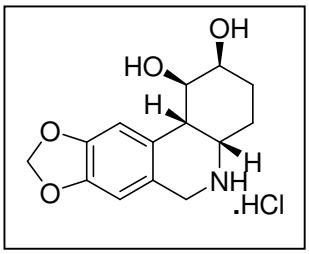
**4,5,5a,6,7,8,9,9a-Octahydro-thieno[2,3-*c*]quinoline-diol hydrochloride 252f-254f ($\Delta^{8,9}$, $\Delta^{7,8}$ and $\Delta^{6,7}$ diol mixture)**




General procedure **Q** was followed using diol mixture **206f-208f** (9 mg, 31 µmol), $CH_2Cl_2$ (2 ml) and TFA (3 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford a mixture of amine hydrochlorides **252f-254f** as a yellow oil (7 mg, 99%).

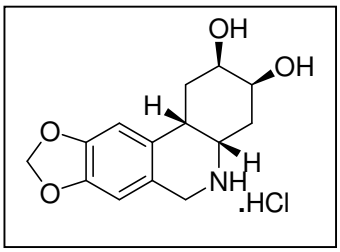
***m/z*** (ESI+) 226 ([M+H]$^+$, 20 %), 225 (11); **HRMS** (ESI+) Found [M+H]$^+$, 226.0899. $C_{11}H_{16}O_2NS$ requires 226.0896.

**(1*RS*,2*SR*,4a*SR*,11b*SR*)-1,2,3,4,4a,5,6,11b-Octahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-1,2-diol hydrochloride 252k ($\Delta^{1,2}$ isomer)**



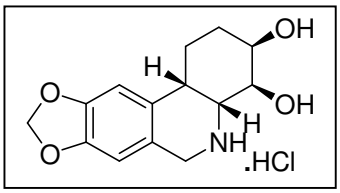

General procedure **Q** was followed using diol **206k** (18 mg, 50 µmol), $CH_2Cl_2$ (2 ml) and TFA (3 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **252k** as a yellow solid (9 mg, 61%). **$^1$H NMR** δ (360 MHz, $D_2O$) 6.76 (1H, s, Ar*H*), 6.57 (1H, s, Ar*H*), 5.80 (2H, s, OC$H_2$O), 4.21-4.12 (2H, m, C$H_2$Ar), 3.95-3.85 (1H, m, C*H*), 3.83-3.75 (2H, m, 2xC*H*), 3.11-3.05 (1H, m, C*H*), 2.04-1.59 (6H, m, 2xC$H_2$+2xO*H*); **$^{13}$C NMR** δ (90.6 MHz, $D_2O$) 147.9 (C), 147.8 (C), 126.6 (C), 121.3 (C), 110.1 (CH), 107.3 (CH), 102.5 ($CH_2$), 71.7 (CH), 68.6 (CH), 52.6 (CH), 44.0 ($CH_2$), 39.6 (CH), 26.0 ($CH_2$), 22.2 ($CH_2$); ***m/z*** (ESI+) 264 ($[M+H]^+$, 4 %), 150 (21), 149 (21); **HRMS** (ESI+) Found $[M+H]^+$, 264.1237. $C_{14}H_{18}O_4N$ requires 264.1230.

**(2*RS*,3*SR*,4a*SR*,11b*SR*)-1,2,3,4,4a,5,6,11b-Octahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-2,3-diol hydrochloride 253k ($\Delta^{2,3}$ isomer)**




General procedure **Q** was followed using diol **207k** (10 mg, 28 µmol), $CH_2Cl_2$ (2 ml) and TFA (3 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **253k** as a yellow solid (7 mg, 81%). **$^1$H NMR** δ (360 MHz, $D_2O$) 6.69 (1H, s, Ar*H*), 6.54 (1H, s, Ar*H*), 5.80-5.79 (2H, m, OC$H_2$O), 4.17-4.09 (2H, m, C$H_2$Ar), 3.79-3.72 (3H, m, 3xC*H*), 3.14-3.11 (1H, m, C*H*), 2.09-1.98 (2H, m, C$H_2$), 1.88-1.72 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $D_2O$) 148.4 (C), 147.6 (C), 129.2 (C), 120.7 (C), 108.8 (CH), 107.3 (CH), 102.5 ($CH_2$), 68.3 (CH), 67.1 (CH), 52.9 (CH), 45.1 ($CH_2$), 34.4 ($CH_2$), 31.9 (CH), 29.8 ($CH_2$); ***m/z*** (ESI+) 264 ($[M+H]^+$, 100 %), 262 (46); **HRMS** (ESI+) Found $[M+H]^+$, 264.1232. $C_{14}H_{18}O_4N$ requires 264.1230.

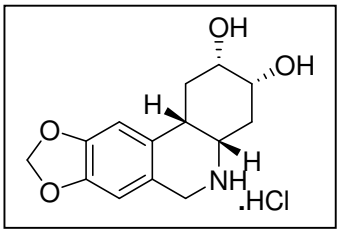
**(3*RS*,4*SR*,4a*RS*,11b*SR*)-1,2,3,4,4a,5,6,11b-Octahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-3,4-diol hydrochloride 254k ($\Delta^{3,4}$ isomer)**




General procedure **Q** was followed using diol **208k** (5 mg, 14 µmol), $CH_2Cl_2$ (2 ml) and TFA (3 ml), then $CH_2Cl_2$ (1 ml) and HCl (2 ml, 1 M in $Et_2O$) to afford amine hydrochloride **254k** as a colourless oil (3 mg, 73%).

**$^1$H NMR** δ (360 MHz, $D_2O$) 6.81 (1H, s, Ar*H*), 6.58 (1H, s, Ar*H*), 5.80 (2H, d, *J* 3.8, OC$H_2$O), 4.16 (1H, d, *J* 16.1, C$H_X$H$_Y$Ar), 4.09 (1H, d, *J* 16.1, CH$_X$$H_Y$Ar), 3.82-3.80 (1H, br s, C*H*), 3.72 (1H, dd, *J* 9.4, 4.5, C*H*), 3.62-3.59 (1H, m, C*H*), 3.22-3.21 (1H, d, *J* 4.5, C*H*), 1.93-1.85 (1H, m, C$H_A$H$_B$), 1.63-1.56 (1H, m, CH$_A$$H_B$), 1.39-1.30 (2H, m, C$H_2$); **$^{13}$C NMR** δ (90.6 MHz, $D_2O$) 149.8 (C), 148.4 (C), 129.1 (C), 123.2 (C), 108.6 (2xCH), 102.1 ($CH_2$), 70.9 (CH), 68.6 (CH), 56.3 (CH), 42.8 ($CH_2$), 35.5 (CH), 27.7 (2x$CH_2$); ***m/z*** (ESI+) 264 ([M+H]$^+$, 24 %), 225 (29), 211 (29), 179 (61); **HRMS** (ESI+) Found [M+H]$^+$, 264.1234. $C_{14}H_{18}O_4N$ requires 264.1230.

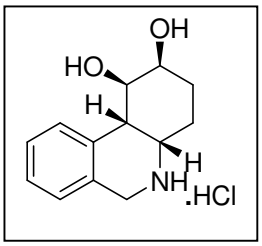
**(2*SR*,3*RS*,4a*SR*,11b*SR*)-1,2,3,4,4a,5,6,11b-Octahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-2,3-diol 255k ($\Delta^{2,3}$ isomer, minor diastereomer)**




General procedure **Q** was followed using *endo-syn* diol **209k** (2.3 mg, 6 µmol), $CH_2Cl_2$ (2 ml) and TFA (3 ml), then $CH_2Cl_2$ (1 ml) and HCl (1 ml, 1M in $Et_2O$) to afford amine hydrochloride **255k** as a colourless oil (1.0 mg, 60%).

**$^1$H NMR** δ (800 MHz, $D_2O$) 6.65 (1H, s, Ar*H*), 6.51 (1H, s, Ar*H*), 5.78 (2H, d, *J* 2.4, OC$H_2$O), 4.08 (2H, s, C$H_2$Ar), 3.91 (1H, d, *J* 2.4, C*H*), 3.72 (1H, ddd, *J* 11.2, 4.0, 2.4, C*H*), 3.49 (1H, s, C*H*), 2.98-2.97 (1H, m, C*H*), 2.14 (1H, dt, *J* 16.0, 3.2, C$H_A$H$_B$), 1.92-1.86 (2H, m, CH$_A$$H_B$+C$H_C$H$_D$), 1.67-1.62 (1H, m, CH$_C$$H_D$); **$^{13}$C NMR** δ (200.0 MHz, $D_2O$) 147.0 (C), 146.4 (C), 129.2 (C), 119.3 (C), 108.0 (CH), 105.9 (CH), 101.2 ($CH_2$), 69.3 (CH), 67.1 (CH), 51.3 (CH), 45.6 ($CH_2$), 35.4 (CH), 32.0 ($CH_2$), 31.7 ($CH_2$); ***m/z*** (ESI+) 264 ([M+H]$^+$, 100 %), 209 (13); **HRMS** (ESI+) Found [M+H]$^+$, 264.1232. $C_{14}H_{18}O_4N$ requires 264.1230.

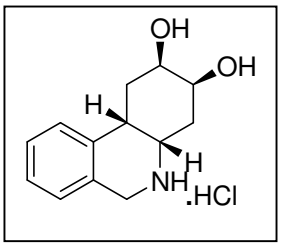
**(1*RS*,2*SR*,4a*SR*,10b*SR*)-1,2,3,4,4a,5,6,10b-Octahydro-phenanthridine-1,2-diol 252m ($\Delta^{1,2}$ isomer)**




General procedure **Q** was followed using diol **206m** (29 mg, 91 µmol), $CH_2Cl_2$ (2 ml) and TFA (3 ml), then $CH_2Cl_2$ (1 ml) and HCl (1 ml, 1 M in $Et_2O$) to afford amine hydrochloride **252m** as a colourless oil (20 mg, 86%).

**$^1$H NMR** δ (360 MHz, $D_2O$) 7.25-7.22 (1H, m, Ar*H*), 7.17-7.13 (2H, m, 2xAr*H*), 7.06-7.04 (1H, m, Ar*H*), 4.28 (1H, *J* 16.2, C$H_X$H$_Y$Ar), 4.21 (1H, d, *J* 16.2, CH$_X$$H_Y$Ar), 3.90 (1H, br d, *J* 7.5, C*H*), 3.75-3.70 (2H, m, 2xC*H*), 3.17 (1H, dd, *J* 7.8, 4.4, C*H*), 1.92-1.85 (1H, m, C$H_A$H$_B$), 1.76-1.70 (1H, m, CH$_A$$H_B$), 1.63-1.56 (2H, m, C$H_2$); **$^{13}$C NMR** δ (62.9 MHz, $D_2O$) 131.9 (C), 129.3 (CH), 128.0 (CH), 127.8 (CH), 127.2 (C), 126.9 (C), 70.5 (CH), 67.7 (CH), 51.6 (CH), 43.0 ($CH_2$), 38.9 (CH), 25.1 ($CH_2$), 21.4 ($CH_2$); ***m/z*** (ESI+) 220 ($[M+H]^+$, 77 %), 219 (29); **HRMS** (ESI+) Found $[M+H]^+$, 220.1331. $C_{13}H_{18}O_2N$ requires 220.1332.

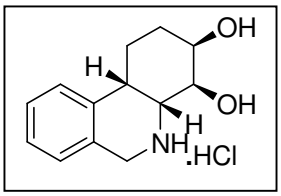
**(2*RS*,3*SR*,4a*SR*,10b*SR*)-1,2,3,4,4a,5,6,10b-Octahydro-phenanthridine-2,3-diol hydrochloride 253m ($\Delta^{2,3}$ isomer)**




General procedure **Q** was followed using diol **207m** (25 mg, 78 µmol), $CH_2Cl_2$ (2 ml) and TFA (3 ml), then $CH_2Cl_2$ (1 ml) and HCl (1 ml, 1 M in $Et_2O$) to afford amine hydrochloride **253m** as a colourless oil (12 mg, 60%).

**$^1$H NMR** δ (360 MHz, $D_2O$) 7.18-7.17 (2H, m, 2xAr*H*), 7.15-7.10 (1H, m, Ar*H*), 7.02 (1H, d, *J* 7.4, Ar*H*), 4.25-4.17 (2H, m, C$H_2$Ar), 3.78-3.70 (3H, m, 3xC*H*), 3.24-3.18 (1H, dt, *J* 10.5, 4.6, C*H*Ar), 2.06-1.97 (2H, m, C$H_2$), 1.85-1.75 (2H, m, C$H_2$); **$^{13}$C NMR** δ (150.8 MHz, $D_2O$) 131.1 (CH), 130.8 (C), 130.0 (CH), 129.4 (C), 129.4 (CH), 129.3 (CH), 70.1 (CH), 68.8 (CH), 54.7 (CH), 46.9 ($CH_2$), 36.1 ($CH_2$), 33.7 (CH), 31.6 ($CH_2$); ***m/z*** (ESI+) 220 ($[M+H]^+$, 100 %), 219 (91), 211 (62), 179 (65); **HRMS** (ESI+) Found $[M+H]^+$, 220.1331. $C_{13}H_{18}O_2N$ requires 220.1332.

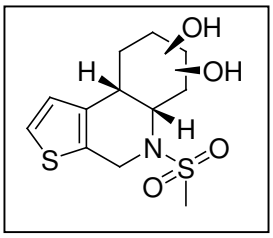
**(3*RS*,4*SR*,4a*RS*,10b*SR*)-1,2,3,4,4a,5,6,10b-Octahydro-phenanthridine-3,4-diol hydrochloride 254m ($\Delta^{3,4}$ isomer)**




General procedure **Q** was followed using diol **208m** (26 mg, 82 μmol), $CH_2Cl_2$ (2 ml) and TFA (3 ml), then $CH_2Cl_2$ (1 ml) and HCl (1 ml, 1 M in $Et_2O$) to afford amine hydrochloride **254m** as a colourless oil 11 mg, 53%.

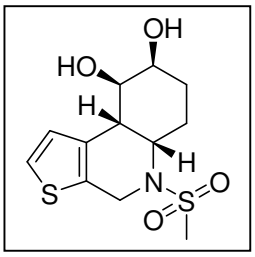
**$^1$H NMR** δ (360 MHz, $D_2O$) 7.29 (1H, d, *J* 6.9, Ar*H*), 7.20 (1H, t, *J* 7.1, Ar*H*), 7.13 (1H, t, *J* 7.6, Ar*H*), 7.05 (1H, d, *J* 7.5, Ar*H*), 4.24 (1H, d, *J* 16.3, C$H_X$H$_Y$Ar), 4.18 (1H, d, *J* 16.3, CH$_X$$H_Y$Ar), 3.79-3.73 (2H, m, 2xC*H*), 3.56 (1H, br d, *J* 9.1, C*H*), 3.33-3.29 (1H, m, C*H*), 2.08-1.97 (1H, m, C$H_A$H$_B$), 1.94-1.85 (1H, m, CH$_A$$H_B$), 1.59-1.53 (1H, m, C$H_C$H$_D$), 1.34-1.26 (1H, m, CH$_C$$H_D$); **$^{13}$C NMR** δ (62.9 MHz, $D_2O$) 133.3 (C), 128.7 (CH), 128.1 (C), 127.4 (CH), 127.0 (CH), 126.8 (CH), 69.0 (CH), 66.7 (CH), 54.5 (CH), 41.3 ($CH_2$), 33.6 (CH), 25.9 ($CH_2$), 21.5 ($CH_2$); ***m/z*** (ESI+) 220 ([M+H]$^+$, 100 %), 218 (21); **HRMS** (ESI+) Found [M+H]$^+$, 220.1331. $C_{13}H_{18}O_2N$ requires 220.1332.

**5-Methanesulfonyl-4,5,5a,6,7,8,9,9a-octahydro-thieno[2,3-*c*]quinoline-diol 256-258**



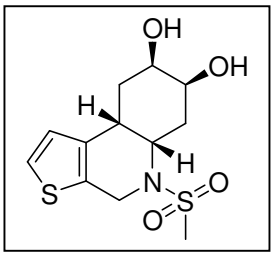
General procedure **P** was followed using phenanthridines **158-160** (15 mg, 56 µmol), THF (312 µl), $H_2O$ (63 µl), $OsO_4$ (49 µl, 2.5% $^{w}/_{w}$ in $^{t}$BuOH, 3.9 µmol) and NMO (20 mg, 0.16 mmol). Flash chromatography ($CH_2Cl_2$-$CH_2Cl_2$:MeOH, 100:2) afforded $\Delta^{1,2}$ diol **256** (1 mg, 6%), $\Delta^{2,3}$ diol **257** (1 mg, 6%), $\Delta^{3,4}$ diol **258** (2.4 mg, 14%), and mixed diol (8 mg, 47%) giving a total yield (12.4 mg, 73%).

**(5a*SR*,8*SR*,9*RS*,9a*SR*)-5-Methanesulfonyl-4,5,5a,6,7,8,9,9a-octahydro-thieno[2,3-*c*]quinoline-8,9-diol 256 ($\Delta^{1,2}$ isomer)**



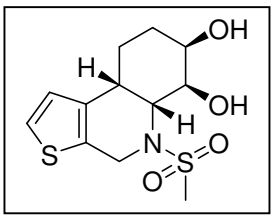
**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.09; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3446 (OH), 2925, 1319, 1151; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.27 (1H, d, *J* 5.3, Het*H*), 6.95 (1H, d, *J* 5.3, Het*H*), 4.81 (1H, dd, *J* 16.8, 1.8, C$H_X$$H_Y$Het), 4.57-4.49 (2H, m, C*H*OH+NC*H*), 4.39 (1H, dd, *J* 17.0, 1.8, $CH_X$$H_Y$Het), 3.59-3.50 (1H, m, C*H*), 3.41 (1H, br s, C*H*), 2.90 (3H, s, $CH_3$), 1.99-1.92 (1H, m, $CH_A$$H_B$), 1.80-1.68 (3H, m, $CH_2$+$CH_A$$H_B$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 131.9 (C), 130.5 (C), 124.5 (CH), 124.4 (CH), 72.0 (CH), 67.6 (CH), 48.6 (CH), 42.1 (CH), 40.7 ($CH_2$), 39.8 ($CH_3$), 26.6 ($CH_2$), 23.4($CH_2$); ***m/z*** (EI) 303 ([M]$^+$, 2 %), 281 (5), 267 (8), 228 (41), 149 (33), 84 (100); **HRMS** (EI) Found: 303.0594. $C_{12}H_{17}O_4NS_2$ requires 303.0594.

**(5a*SR*,7*SR*,8*RS*,9a*SR*)-5-Methanesulfonyl-4,5,5a,6,7,8,9,9a-octahydro-thieno[2,3-*c*]quinoline-7,8-diol 257 ($\Delta^{2,3}$ isomer)**




**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.09; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3396 (OH), 2927, 1661, 1319, 1151; **$^1$H NMR** δ (250 MHz, $CDCl_3$) 7.25 (1H, d, *J* 5.3, Het*H*), 7.01 (1H, d, *J* 5.0, Het*H*), 4.83 (1H, dt, *J* 17.0, 0.8, C$H_X$H$_Y$Het), 4.43 (1H, dd, *J* 12.3, 4.8, NC*H*), 4.34 (1H, dd, *J* 16.8, 3.5, CH$_X$$H_Y$Het), 3.98 (1H, s, C*H*OH), 3.55-3.46 (1H, m, NCHC*H*), 3.27 (1H, br s, C*H*OH), 2.89 (3H, s, C$H_3$), 2.29-2.20 (2H, m, C$H_2$), 2.04-1.93 (1H, m, CH$_A$$H_B$), 1.87-1.75 (1H, m, C$H_C$H$_D$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 134.7 (C), 129.8 (C), 125.0 (CH), 124.1 (CH), 69.2 (CH), 66.8 (CH), 47.8 (CH), 40.6 ($CH_2$), 39.7 ($CH_3$), 35.4 (CH), 30.5 ($CH_2$), 30.3 ($CH_2$); ***m/z*** (EI) 303 ([M]$^+$, 5 %), 285 (18), 224 (67), 206 (36), 178 (23), 149 (32), 136 (100); **HRMS** (EI) Found: 303.0593. $C_{12}H_{17}O_4NS_2$ requires 303.0594.

**(5a*RS*,6*SR*,7*RS*,9a*SR*)-5-Methanesulfonyl-4,5,5a,6,7,8,9,9a-octahydro-thieno[2,3-*c*]quinoline-6,7-diol 258 ($\Delta^{3,4}$ isomer)**




**$R_f$** [$CH_2Cl_2$:MeOH, 9:1] = 0.11; **$\upsilon_{max}$** ($CHCl_3$)/$cm^{-1}$ 3446 (OH), 2929, 1649, 1315, 1149; **$^1$H NMR** δ (360 MHz, $CDCl_3$) 7.22 (1H, d, *J* 7.6, Het*H*), 6.90 (1H, d, *J* 7.2, Het*H*), 4.92 (1H, dd, *J* 24.5, 2.2, C$H_X$H$_Y$Het), 4.43 (1H, dd, *J* 24.2, 2.9, CH$_X$$H_Y$Het), 4.33 (1H, dd, *J* 14.8, 7.9, NC*H*), 4.06 (1H, d, *J* 4.0, C*H*OH), 3.55 (1H, dd, *J* 14.8, 4.3, NCHC*H*), 3.28 (1H, br s, C*H*OH), 2.98 (3H, s, C$H_3$), 2.26-2.16 (1H, m, C$H_A$H$_B$), 2.09-2.01 (1H, m, CH$_A$$H_B$), 1.83-1.75 (1H, m, C$H_C$H$_D$), 1.40-1.32 (1H, m, CH$_C$$H_D$); **$^{13}$C NMR** δ (90.6 MHz, $CDCl_3$) 135.3 (C), 130.2 (C), 124.7 (CH), 124.0 (CH), 69.1 (CH), 67.4 ($CH_2$), 55.2 (CH), 40.7 ($CH_2$), 39.6 ($CH_3$), 36.1 (CH), 25.6 ($CH_2$), 21.7 ($CH_2$); ***m/z*** (EI) 303 ([M]$^+$, 6 %), 285 (20), 228 (22), 224 (100), 206 (52); **HRMS** (EI) Found: 303.0588. $C_{12}H_{17}O_4NS_2$ requires 303.0594.

**General Procedure R - Zebrafish phenotype screening**

The following protocol was used for the preliminary wild-type screening of our compound library.[172]

1) Chemicals were diluted into the E3 screening medium. Aliquots of 200 µl (or multiples thereof) were prepared at concentrations ranging from 100 µM to 1 µM, all with 0.5% $^{v}/_{v}$ DMSO. When not in use the aliquots were stored in the freezer.
2) Five small breeding tanks were set up in the evening, each containing one male zebrafish and one or two females. The tanks were kept in darkness until the next morning when the lights were switched on causing the fish to breed.
3) The embryos were collected, pooled and washed with E3 medium. Dead, delayed or unformed embryos were discarded, and the adult fish were returned to their main tank.
4) The embryos were divided into two petri dishes and stored in an incubator at 28.5 $^{o}$C until required.
5) The chemical aliquots were placed in the same incubator to defrost.
6) Once the embryos had reached the desired age they were distributed in 96-well plates as appropriate to the screen, with two or three embryos per well.
7) The surrounding medium was removed from the embryos using a wide-tipped Pasteur pipette and then the appropriate 200 µl chemical aliquot was added to the well. Four control wells were used per plate, each containing E3 with 0.5% $^{v}/_{v}$ DMSO.
8) The plates were incubated at 28.5 $^{o}$C and examined periodically over the next five days using a microscope to assess any phenotypes. Photographs were taken where required using a digital camera coupled to a microscope.
9) At 5 dpf the embryos were disposed of.

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# ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl or acetate |
| AIBN | azobisisobutyronitrile |
| aq | aqueous |
| Ar | aryl |
| BIOS | biology oriented synthesis |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Bu | butyl |
| CAN | ceric ammonium nitrate |
| Cbz | carbobenzyloxy |
| CsOH | caesium hydroxide |
| COSY | correlation spectroscopy |
| Cy | cyclohexyl |
| DCC | dicyclohexylcarbodiimide |
| dba | dibenzylideneacetone |
| DBDMH | 1,3-dibromo-5,5-dimethylhydantoin |
| DMA | *N*,*N*-dimethylacetamide |
| DMDO | dimethyldioxirane |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMAP | dimethylaminopyridine |
| DMSO | dimethylsulfoxide |
| dr | diastereomeric ratio |
| DOS | diversity-oriented synthesis |
| dpf | days post fertilisation |
| dppa | diphenylphosphorylazide |
| $EC_{50}$ | concentration of agonist required to produce 50% of the maximal response |
| EI | electron impact ionisation |
| eq | equivalent |
| ESI | electrospray ionisation |
| Et | ethyl |
| FAB | fast atom bombardment |
| FDA | food and drug administration |
| FVP | flash vacuum pyrolysis |
| h | hour |
| HB | Herrmann-Beller |
| HMDS | hexamethyldisilazide |
| hpf | hours post fertilisation |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrum |
| HSQC | heteronuclear single quantum correlation spectroscopy |
| IR | infra red |
| LDA | lithium diisopropylamide |
| mCPBA | *meta*-chloroperoxybenzoic acid |

| | |
|---|---|
| Me | methyl |
| µwave | microwave |
| mins | minutes |
| MP | melting point |
| MRSA | methicillin-resistant staphylococcus aureus |
| NBS | *N*-bromosuccinimide |
| NMO | *N*-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| 3-NOBA | 3-nitrobenzylalcohol |
| NOESY | nuclear Overhauser effect spectroscopy |
| P | unspecified protecting group |
| PCA | principal component analysis |
| PMB | 4-methoxylbenzyl |
| ppm | parts per million |
| PPTS | pyridinium *para*-toluenesulfonate |
| Pr | propyl |
| Poc | propargyloxy |
| PSSC | protein structure similarity clustering |
| py | pyridine |
| RCM | ring closing metathesis |
| ROM | ring opening metathesis |
| ROMP | ring opening metathesis polymerisation |
| RRM | ring rearrangement metathesis |
| $R_f$ | retention factor |
| r.t. | room temperature |
| $R_t$ | retention time |
| sat | saturated |
| SCONP | structural classification of natural products |
| TBAF | tetrabutylammonium fluoride |
| TBAI | tetrabutylammonium iodide |
| TFA | trifluoroacetic acid |
| THIOG | thioglycerol |
| TLC | thin layer chromatography |
| THF | tetrahydrofuran |
| TMS | trimethylsilyl |
| TOS | target-oriented synthesis |

# APPENDIX

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